Universidade de Lisboa

Faculdade de Farmácia

Influence of country-specific data on the results of cost-effectiveness analysis of novel oral anticoagulants in atrial fibrillation

Miguel Arcanjo Resende Martins de Teixeira

Mestrado Integrado em Ciências Farmacêuticas

2017

Universidade de Lisboa
Faculdade de Farmácia

Influence of country-specific data on the results of cost-effectiveness analysis of novel oral anticoagulants in atrial fibrillation

Miguel Arcanjo Resende Martins de Teixeira

Monografia de Mestrado Integrado em Ciências Farmacêuticas apresentada à Universidade de Lisboa através da Faculdade de Farmácia

Supervisora: Professora Doutora Sofia Oliveira Martins, Professora Assistente, Faculdade de Farmácia da Universidade de Lisboa;

Orientador: Andrej Janžič, PhD, Faculdade de Farmácia da Universidade de Ljubljana;

Co-orientador: Mitja Kos, PhD, Faculdade de Farmácia da Universidade de Ljubljana;

2017

Resumo

Os novos anticoagulantes orais foram aprovados para comercialização na Europa pela Agência Europeia do Medicamento entre 2008 e 2011. Estes prometem ser uma alteração importante que permitirá mais segurança (por apresentarem menos interações com outros fármacos e com alimentos) e comodidade aos doentes dado não ser necessário monitorizar a razão normalizada internacional (INR), como no caso da Varfarina. Existem, no entanto, três fármacos desta classe no mercado. Qual deles será o mais custo efetivo em doentes com fibrilação auricular? Vários estudos debruçam-se sobre esta questão em vários países europeus, nomeadamente em Portugal, Eslovénia, Suécia, Holanda e no Reino Unido. O presente trabalho procura avaliar o custo-efetividade dos novos anticoagulantes orais (Apixabano, Dabigatrano e Rivaroxabano) em comparação com a Varfarina na fibrilação auricular nos 5 países europeus mencionados anteriormente. De notar que no caso da Suécia apenas o Apixabano foi avaliado. Para tal, foi utilizada uma mesma árvore de Markov e um mesmo software informático (TreeAgePRO) para realizar as análises custo-efetividade (mais propriamente custo-utilidade) necessárias minimizando assim diferenças entre países provocadas pelas próprias particularidades do estudo, pelo modelo de Markov escolhido, entre outros. Avaliou-se não só qual o novo anticoagulante oral mais custo-efetivo por país recorrendo ao Incremental Cost-Effectiveness Ratio (ICER) mas também a influencia relativa de cada um dos parâmetros necessários para realizar as analises: parâmetros Baseline, Custo dos fármacos, Custo total (custo dos fármacos + custo dos eventos), Tabelas de Mortalidade e Utilidades.

Para realizar o estudo foi então necessário reunir toda a informação necessária a introduzir no modelo através do software já mencionado. Esta foi recolhida sobretudo de 4 artigos sendo cada um referente a um país, exceto no caso da Holanda e do Reino Unido em que o mesmo artigo foi utilizado para ambos, visto este já ser sobre os dois. A restante informação, (nomeadamente as tabelas de mortalidade) foi obtida de organismos estatais ou de fontes relevantes destes dados para os países em causa.

Depois de obtida a informação esta foi compilada em tabelas com as variáveis necessárias para realizar a analise. Vários valores tiverem de ser ajustados por método de cálculo ou outro ajuste relevante para que os mesmos pudessem ser introduzidos no modelo. No caso de um ou outro valor desconhecido para um determinado país utilizou-se o valor mais adequado: ou um valor semelhante no caso, por exemplo, dos vários graus de doença ou o valor referencia do estudo original proveniente do artigo: “Cost Effectiveness of Novel Oral Anticoagulants for Stroke Prevention in Atrial Fibrillation Depending on the Quality of Warfarin Anticoagulation Control” por Andrej Janžič e Mitja Kos (2014).

A árvore de Markov utilizada foi uma ligeira adaptação da utilizada no artigo acima mencionado. As diferenças prendem-se com a exclusão deste estudo do fármaco Edoxabano e da Varfarina quando o seu doseamento é ajustado tendo em consideração a genotipagem.

Seis tipos de análise foram realizadas, para cada um dos fármacos, em cada um dos cinco países tendo como base os dados provenientes do artigo já mencionado acima: alterando somente os custos dos fármacos para os custos destes em cada país; alterando o custo dos fármacos e dos eventos para os de cada país; alterando somente as tabelas de mortalidade para as de cada país; alterando somente as utilidades para as de cada país; alterando todos os dados para os dados específicos de cada país exceto as tabelas de mortalidade; alterando todos os dados para os dados específicos de cada país. Isto permitiu não só no final obter o custo-efetividade de cada um dos fármacos nos países em causa, mas também determinar a influencia relativa que cada um dos tipos de variáveis (já mencionadas) tem no resultado final.

Os gráficos de custo-utilidade (Custo (€) x QALY) foram obtidos e analisados para os 5 países e para os 4 medicamentos (incluindo a Varfarina e excluindo o Dabigatrano e o Rivaroxabano no caso da Suécia).

Observou-se que os custos dos eventos têm um impacto muito grande no custo simulado final apresentando um impacto relativo maior que o próprio custo dos medicamentos. Isto tem real importância dadas as variações destes custos (dos eventos) nos vários países estudados.

Ficou também patente que o custo simulado final era bastante influenciado pelas Tabelas de Mortalidade e pelas respetivas probabilidades de morte nas idades relevantes para o modelo utilizado. No entanto, esta influencia é inferior relativamente à do custo dos eventos já mencionada.

No que toca à efetividade simulada final esta é relativamente mais influenciada pelas tabelas de mortalidade do que pelas utilidades em si, visto estas não serem assim tão diferentes de país para país ao contrário das probabilidades de morte sobretudo entre os 70 e os 85 anos, intervalo que é utilizado pelo modelo e onde se verificam diferenças grandes entre os países estudados sendo que neste parâmetro a Suécia apresenta um grande aumento da efetividade em QALY por apresentar a menor probabilidade de morte neste intervalo.

Focando a analise nos fármacos em si é possível concluir que o Rivaroxabano apresenta o custo simulado final mais elevado para todos os países em que foi analisado e que em termos de efetividade aproxima-se mais da Varfarina do que propriamente dos restantes Novos Anticoagulantes Orais. É também interessante denotar que o custo simulado final da Varfarina é maior na Suécia, Holanda e no Reino Unido que o custo simulado final dos novos anticoagulantes orais Apixabano e Dabigatrano em Portugal e na Eslovénia. Já o Apixabano e o Dabigatrano

apresentam resultados simulados finais mais próximos um do outro no que concerne tanto ao custo como à efetividade.

Como já foi referido, para definir o Novo Anticoagulante Oral mais custo-efetivo (exceto na Suécia onde foi apenas comparada a Varfarina com o Apixabano) é necessário recorrer ao ICER. Os resultados deste mostram que o Apixabano é o Novo Anticoagulante Oral mais custo-efetivo em Portugal, na Eslovénia e na Holanda enquanto que, o Dabigatrano provou ser mais custo-efetivo no Reino Unido. Em sentido oposto o Rivaroxabano mostrou um custo por QALY muito elevado superior ao limiar normalmente utilizado por decisores para decidir sobre a comparticipação ou não de um fármaco de 20000€/QALY.

Analisando de uma forma mais transversal o custo por QALY entre os vários países para um mesmo medicamento é importante referir que a Suécia apresenta o menor custo por QALY no caso do Apixabano, o que é um bom sinal apesar de não ser possível com os dados recolhidos saber qual o Novo Anticoagulante Oral mais custo-efetivo neste país.

É possível ainda denotar uma diferença no Custo por QALY (excluindo o Rivaroxabano) entre dois grupos de países. Este é muito mais baixo em países teoricamente tidos como mais desenvolvidos (Holanda, Suécia e Reino Unido) que em Portugal e na Eslovénia.

Neste estudo é também feita uma referência às limitações do mesmo, explorando de forma coerente as que podem ou não ter impacto nos resultados aqui já mencionados nomeadamente os períodos de tempo a que se referem as tabelas de mortalidade, alguns dos valores ajustados para determinadas variáveis, a atualidade do mesmo (visto que os dados foram recolhidos de artigos publicados entre 2014 e 2015), bem como outros relacionados com os custos dos eventos e fármacos recolhidos, entre outros.

Nas conclusões são ainda nomeadas algumas hipóteses para as possíveis causas estruturais que levam a alguns dos resultados obtidos no decorrer deste estudo.

Palavras-chave: Custo-efetividade; Anticoagulantes; Quality-adjusted life years; Fibrilação auricular; Incremental Cost-effectiveness ratio.

Abstract

Background From 2008 on, Novel Oral Anticoagulants are available on the European market. These offer an alternative to Warfarin in stroke prophylaxis in patients with atrial fibrillation. They present the advantage that they don't need regular monitoring and have less interaction with both other medicines and food. The aim of this study is to understand which of the Novel Oral anticoagulant drug is more cost-effective in 5 different European countries, as well as understand which variables have more impact in the differences between the overall result of cost-effectiveness in these 5 settings.

Methods An adaptation of a Markov decision model based on one from the article: "Cost Effectiveness of Novel Oral Anticoagulants for Stroke Prevention in Atrial Fibrillation Depending on the Quality of Warfarin Anticoagulation Control" by Andrej Janžič and Mitja Kos (2014), was made. This allowed to answer the questions raised and mentioned before by performing the analyses for the 4 drugs (Warfarin, Apixaban, Dabigatran and Rivaroxaban) on the 5 countries (Slovenia, Portugal, Sweden, The Netherlands and the United Kingdom) under the same model. Six types of simulations were run having the Slovenian parameters has reference: 1 – Changing only the drug costs to the ones from each country; 2 – changing all the costs for the national-specific ones (event costs + drug costs); 3 – using only the national-specific life tables; 4 – using only the national-specific utilities and monthly disutilities; 5 – using all national-specific data except the life tables; 5 -using all the national-specific data. The cost-effectiveness analysis, more specifically the cost-utility analysis were made from each State's healthcare payer perspective.

Results Through Incremental Cost-effectiveness Ratio it was possible to conclude that Apixaban was the most cost-effective of the Novel Oral Anticoagulants in Slovenia, Portugal and The Netherlands while Dabigatran proved to be more cost-effective in the United Kingdom. It was also shown that event cost had relatively more impact that drug costs in the overall cost-effectiveness result for each country than drug costs. Life tables also had a great impact in the effectiveness outcome of each country. Countries with lower death probabilities in individuals from 79- to 85 years-old had higher effectiveness outcomes.

Conclusion The Cost per Quality-adjusted Life Year varies highly between different European healthcare settings and mostly because of event costs and mortality tables. Also all of the Novel Oral Anticoagulant Drugs Incremental Cost-effectiveness Ratio were under the common reimbursement threshold of 20000€ per Quality-adjusted Life Year except for Rivaroxaban.

Keywords: Cost-effectiveness; Anticoagulants; Qaulity-adjusted life years; Atrial fibrillation; Incremental Cost-efectiveness ratio.

“The only place Success comes before Work is in the Dictionary.”

- Vince Lombardi

To my Mother and Brother…

Acknowledgements:

Throughout the process of doing this Master Thesis a certain number of people and entities had a very important role and it was impossible to complete this work without acknowledging them one by one.

First, I would like to thank the Chair of Social Pharmacy at the Faculty of Pharmacy, University of Ljubljana in the person of Mitja Kos for receiving me in a way I will never forget and for the help during the ERASMUS+ Program that culminated with the writing of this thesis. I would also like to address special thanks to Andrej Janžič for all the insights, help, patience and availability he demonstrated.

Second, I would like to thank the Faculty of Pharmacy, University of Lisbon for the amazing 5 years I spent there. Specially in the case of this thesis to Dra. Sofia Oliveira Martins for her supervision, effort and guidance during the process.

I would also like to thank my incredible Mother and Brother who stood by my side no matter what and surely had the most important role throughout this adventure. All I achieved is yours, because without you, it was simply impossible.

To my father, who always gave me words of courage and perseverance to finish this work and to whom I owe a lot, especially in this last year.

To my family for the unconditional support, love and patience.

To Inês for all the, love, support, help, patience, guidance, kindness and serenity she empowered me with. Without you this was also not possible and to that and for that, I thank you!

To my most dedicated friends: Guilherme Silva and Nuno Navega who helped ease the pressure all along this 5 years.

I also must acknowledge a special kind of friends, those who even tough were battling with me the same fights for roughly 5 years never let me down and were always there to help: thank you Diana Branco, Joana Craveiro and Guilherme Lopes.

To Joana for her decisive help and her parents Raúl and Luísa for far more that I could ever repay, I am truthfully grateful.

Last, but not least, I must thank the biggest and most magnanimous Institution I ever was part of and everyone there for their companion, relaxation, crazy adventures, but most of all friendship and guidance in the making of this thesis!

Abreviations

ALLC – All Costs (Drug Costs plus Event Costs);

ALLUT – All Utilities;

AF – Atrial Fibrillation;

ARISTOTLE - Apixaban for Reduction in Stroke and other Thromboembolic Events in Atrial Fibrillation;

CE – Cost-effectiveness;

DALY – Disability-adjusted Life Year;

DC – Drug Costs

EMA – European Medicines Agency

EQ-5D – EuroQol – 5D

EuroQol – European Quality of Life Scale;

FDA – Food and Drug Administration, United States of America;

ICER – Incremental Cost-effectiveness Ratio;

INR – International Normalized Ratio;

HUI – Health Utilities Index;

HYE – Health Year Equivalent;

INFARMED – Infarmed, Autoridade Nacional do Medicamento e Produtos de Saúde, I. P., Portugal;

LYG – Life Years Gained

MT – Mortality Tables (Life Tables);

NAM – National Adopted Model;

NICE – National Institute for Health and Care Excellence, United Kindgdom;

NOAC – Novel Oral Anticoagulant Drug;

NOACs – Novel Oral Anticoagulant Drugs;

OBC – Other Baseline Characteristics;

QALY – Quality-adjusted Life Years;

RE-LY - Randomized Evaluation of Long-Term Anticoagulation Therapy;

ROCKET-AF - Rivaroxaban Once-daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation;

TTR – Time in Therapeutic Range;

UK – United Kingdom of Great Britain;

WHO – World Health Organization;

WTP – Willingness-to-pay;

Table of Contents:

List of Figures:

List of Tables:

1 Introduction

1.1 Definitions and Basic Concepts

1.1.1 Health Economics

To fully understand Pharmacoeconomics and Cost-effectiveness (CE) evaluations, one must understand the importance of Health Economics in the present World. It is of paramount importance to first comprehend the concepts and features of health economics and how they matter to States and to Society.

1.1.1.1 Health, Economics and Health Economics

The first concept that must be addressed is Health. What is Health after all?

According to the WHO, Health is state of complete physical, mental and social well-being and not merely the absence of disease or infirmity(1). Even though it is a definition from 1946 this one is regarded as the best and simplest definition for Health. Nevertheless, when we think about health and its dimension and projections into the economics field, the definition might be slightly different. Health in health economics stands for everything that is related to means, ways, systems, societal strategies and others that contribute to the state of health described in the WHO definition for a particular group of people.

On the other hand, Economics still has nowadays a big variety of accepted definitions(2).

The definition of economics evolved throughout the centuries, since Scottish philosopher Adam Smith defined it for the first time in 1776 as “a branch of the science of a statesman or legislator [with the twofold objectives of providing] a plentiful revenue or subsistence for the people ... [and] to supply the state or commonwealth with a revenue for the public services”(3,4).

After this, others like Stuart Mill and Thomas Carlyle described in their way what was economics(5,6), but it was only with Alfred Marshall in his textbook: Principles of Economics (1890) that for the first time the definition of economics extended analysis beyond wealth and the societal level into the microeconomic level(7). Still, in the 20th Century the definition of economics continues to evolve and one of the most commonly accepted definitions is the one from 1932 by the English economist Lionel Robbins where economics is defined as: “a science which studies human behaviour as a relationship between ends and scarce means which have alternative uses”.(8)

Lionel Robbins was the first to publicly state that the economics domain was more than just wealth and markets, and until the 1960´s, when the economic theory of maximizing behaviour and rational-

choice modelling expanded the domain of the subject to areas previously treated in other fields he was very criticized for failing to limit the subject to the analysis of wealth and above all, markets(9).

It was this idea of economics, in which you can relate the subject to other domains, and where managing scarce resources(10) is also an important matter that opened the way to more specific areas like health economics to appear and thrive, especially in the 21st century where societies manage limited resources and where health and healthcare are a considerable cut of every country's annual budget.

It is though, the 2005 definition of economics given in an introductory textbook by Begg, Fischer and Dornbusch that is considered more instructive and easier to understand.

According to this textbook Health Economics is defined as "the study of how society decides what, how and for whom to produce". In this definition health care is considered a manufacturable good/service as in any other area(11) but you can still relate it to healthcare as we can see on the 2012 definition by Morris, Devlin and Parkin: "Health economics is the application of economic theory, models and empirical techniques to the analysis of decision-making by individuals, health care providers and governments with respect to health and healthcare"(12).

1.1.1.2 Concepts of Health Economics: Production, Resources, Scarcity and Opportunity Cost.

As we have seen in the more recent definitions above, health care is regarded as a good or service that can be manufactured or produced. Like all other produced goods and services health and health care also need resources and therefore production can be regarded as the process by which these resources are transformed into goods:

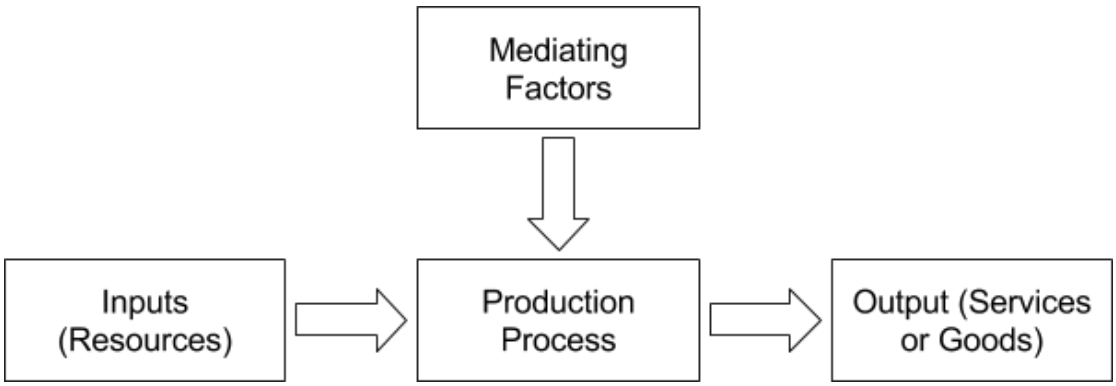


Figure 1 – Schematic definition of Economics, applicable to Health Economics (adapted from Public Health Textbook, 4d Health Economics, Parkins D., 2009) (13)

For example, specifically in health economics, the resources can be the personnel (labor), equipment, a medicine/drug, buildings (capital) or raw materials. The output production in health care can be for example the amount of healthcare provided of a given quality with a specific group of inputs like health care professionals, therapeutic material and a clinic. We can also relate to the pharmaceutical area if we think that a medicine/drug and a group of people with the same condition are the input, the production process is the treatment and the outcome is the benefit to a patient or a group of patients treated with that particular drug. Mediating factors, are factors by which the production can be affected positively or negatively, such as if the clinic in the study is public or privately owned or if, for instance, a medicine has state reimbursement or not(13).

Basically, in health economics the key factor is that resources are known to be limited in quantity and that it is not exactly known what is the desired quantity of outputs. This has two consequences: the first is easy to understand and it is the fact that this then acts as the fundamental driving force for the economic activity; the second is that explains the reason health care should be considered like other goods. The issue described above is known as the "scarcity of resources" and this determines that choices must be made in health care on what, how and for whom health care is provided (produced).

Summarizing, health care is an economic good because the resources consumed to provide it are limited and one society can only use more resources to provide health care if it diverts more resources from other areas and because a society's true demand for health care in the absence of constraints on its ability to pay for it is not known(13).

Other important concept in economics and in health economics is the opportunity cost which is slightly different from the normal definition of cost (financial cost) people are used to.

Basically, in economics every time a choice must be made between mutually exclusive alternatives, the opportunity cost is the "cost" (benefit or lack of it) incurred by not choosing the second best available choice/alternative or "the loss of potential gain from other alternatives when one alternative is chosen(14–16).

1.1.1.3 Distinctive features of Healthcare Economics

It is nowadays a scientific consensus that health care economics has features that make it different from normal economics. A lot of authors have written about it since the 50's like Mushkin (1958)(17), Klarman (1963)(18), Culyer (1971)(19), Pauly (1978, 1988)(20,21) and Folland et al. (1993)(22) but the differences between economics and health economics were always a hard subject to write about and the question: "Is health care different?" remained without a clear answer for a

long time. Despite this, as written before, a consensus has been reached and it is postulated that health care economics has four main features that all together make it unique because even though they can be found in other economic areas they cannot be found together and to the extent they are present in the health care economics area.

These four features are: (1) the demand for health care is a derived demand (for health); (2) Externalities; (3) Informational asymmetries between patients and providers; (4) Uncertainty with respect to both the need for and the effectiveness of health care(23).

1.1.1.3.1 Derived demand for Healthcare

Health care is a conditional desirable good that is consumed in order to improve health. This makes that unlike many other goods that are consumed for their direct properties, health care is consumed to produce health(24).

Health care is not at every moment a desirable good, becoming only desirable in case of illness nor it is always perceived as good because its direct effects sometimes decrease utility (e.g. pain after a treatment/intervention).

In the end health care only becomes a desirable good when ultimately its effect on health outweighs its short term direct negative effects(23).

1.1.1.3.2 Externalities

An externality is any impact, positive or negative that affects other people outside of the particular parties involved in an exchange.

In health care, externalities are very important especially the ones related to health care given to others because one benefits from the fact that other people are healthy because that decreases the likelihood of you getting sick (if it is contagious).

Other examples can be: health care produces a great deal of chemical waste, produces a great deal of emissions (ambulances, etc.) and alters the natural ecological environment of bacteria (negative), the fact that because of the way our health care works we are altering the resistance patterns of bacteria (negative), the fact that health creates wealth because healthy workers are more productive and they are less absent from work (positive) or vaccination where herd immunization can prevent a big group of people to get sick from a particular disease (positive)(23).

1.1.1.3.3 Informational asymmetries

These informational asymmetries are very important in health care and they have an impact on the way people perceive health systems and in the way they are structured. Even though there are efforts in place to try to minimize these discrepancies, they are still present.

The hardest asymmetry to counterbalance and the most important one for the patient has to do with the patient knowing much more about what he feels but still relying on the health care professional to be diagnosed and be treated. This can lead to a variety of situations where resources are wasted because the patient doesn't understand the severity of his/her condition and quits the treatment earlier only to come back later in need of more specialized and expensive therapies. Also, some health care professionals can take advantage of their patients because some of these matters are too complex even for the patient to realize he is being deceived or misled(25).

The second most important asymmetry, if not the most important is between healthcare professionals and health policy makers. Most of health policies are decided and approved by people who even though they are nowadays progressively more informed, most of the times still lack the health professional background or the health technical skills and views. This makes them more easily influenced and deceived by corporate and other interests and not buy patient health needs(23).

1.1.1.3.4 Uncertainty with respect to both the need for and the effectiveness of Healthcare

In 1963 American economist Kenneth Arrow identified two important types of uncertainty that could be found in the healthcare market: the uncertainty in the demand for health care and the uncertainty regarding the effectiveness of treatment. From this it is possible to understand that illness have a random component and therefore also the individual demand for health care and the effectiveness of treatments also have a considerable random factor that cannot be fully measured or analysed(23,26).

This ultimately means that even thorough studies and decisions based upon them may not fully work on everyone or in every society because of this uncertainty, both from the diseases and individuals.

1.1.1.4 The importance of Health Economics

Health economics is becoming increasingly important as governments and national health care policy makers must manage limited resources. With this, the States use economic assessment and evaluations to predict if the purchase of a equipment or drug, or if the construction of a hospital or,

for instance, if hiring more doctors will be cost-effective. This means decision makers are taking measures to reduce the risk of spending money that in fact doesn't benefit the health of their citizens by reducing the risk of the decisions they make(27,28).

Health economics helps reducing this risk because the studies and evaluations that are possible to make allow for more informed and rational decisions and policies. Accordingly, health economics is very important as it empowers governments with vital information that allows for health systems to be sustainable and efficient through the detailed assessment of each particular case leading to an allocation of resources that suits better the needs of the health system and the people in particular.

This more detailed analysis made by decision makers also leads the industry to rely on health economic assessments, because a drug or medical device can only be profitable if it is cost-effective or a major breakthrough(27).

Health economics is also very important in insurance markets because only a great level of knowledge of the health market allows for more profitable insurances and, these companies rely heavily on economic evaluations to maintain or increase their level of profit.

So, as we can understand, health economics is important to many stakeholders in many ways and it is mostly relevant to state agencies that manage health care on their respective countries, as it results in better policy making that favours ultimately their own citizens/taxpayers(29).

1.1.2 Pharmacoeconomics

Pharmacoeconomics is a fusion of Pharmacy and Economics and therefore a subset of Health Economics that can be defined as a "social science concerned with the description and analysis of the costs of pharmaceutical products and their impact on individuals, health care systems, and society"(30).

This area of expertise evolved to measure the value of patient care provided whilst ensuring an efficient use of resources. Due to this factor Pharmacoeconomics relates to health care services in general not being strictly restricted to pharmaceutical products.

Nonetheless patient care must retain the quality standards considered reasonable even when controlling and/or restraining costs. The aim is that products and health care services provided by a certain group of professionals demonstrates pharmacoeconomic value. Pharmacoeconomic value is a balance between the outcomes involved: economic, humanistic (e.g., quality of life) and clinical (e.g., presence of disease).

It is the role of Pharmacoeconomics to study and provide ways to quantify this value(31).

As described before Pharmacoeconomics needs to access the clinical outcomes of healthcare and, due to this Pharmacoeconomics can also be considered a subset of outcomes research that encompasses pharmaceuticals and economic outcomes.

1.1.3 Types of Pharmacoeconomic Evaluation

There are essentially two types of pharmacoeconomic evaluation: cost analysis and cost-outcomes analysis. In the first one the focus resides on the costs of providing health care services. In the second, the result is a ratio between the cost of certain health care services and their clinical and humanistic outcomes(30).

The next table presents a clear view over the most common methodologies showing that the endpoint of each methodology is the same (ratio between costs and outcomes) but expressed in different ways:

Table 1 – Types of Pharmacoeconomic Evaluation (adapted from: Pharmacoeconomics: A Primer for the Pharmaceutical Industry, Alan Morrison, Albert Wertheimer, 2002)(30)

Method of Analysis	**Cost Measure**	**Outcome Measure**
Cost Analysis		
Cost-of-Care	Currency	Not Applicable
Cost-Outcomes Analysis		
Cost-Effectiveness	Currency	Natural Units (e.g.: life-years gained “LYG”)
Cost-Utility*	Currency	Utilities, usually QALY
Cost-Benefit	Currency	Currency
Cost-Minimization	Currency	Natural units or utilities
* special case of CE analysis		

In this study it will be used the CE analysis, more specifically the cost-utility analysis. The focus of the next two sections will be about these two methods.

1.1.3.1 Cost-effectiveness: Basic Concepts

1.1.3.1.1 Decision Analysis and Decision Trees

Decision Analysis is the core of a CE analysis. It "involves using specific tools and mathematical models to identify, assess, and represent key features of a decision"(32). Each alternative will then have a probability of occurring and this way it is possible to weight all the variables against their risk or rewards of occurring by decomposing a complex structure of decision into a simple decision tree where each branch represents a different outcome (possible decision, occurrence or reaction) with a different chance of happening(33).

The decision tree is then a diagrammatic representation of this complex algorithm around the decision itself that represents it in an effective and easy way to fully understand the potential courses of action of a decision and its range of possible outcomes(30).

The tree consists of branches (lines) and nodes: decision nodes (square), chance nodes (circular) and terminal nodes (triangular). The chance nodes together with branches connect the decision nodes with the terminal ones. Each of the branches deriving from the chance node will then have a probability of occurrence, and the sum of these will have to be one.

The next figure shows a simple decision tree:

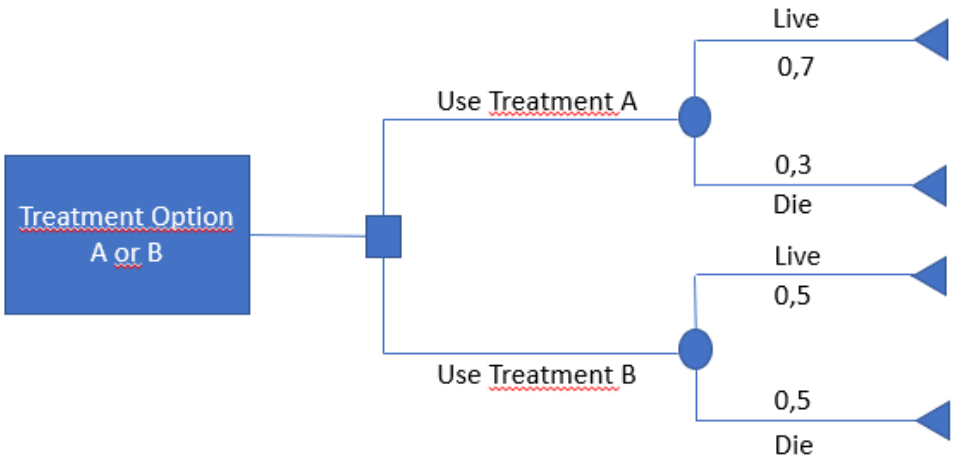


Figure 2 – Simple Decision Tree Example (adapted from: Pharmacoeconomics: A Primer for the Pharmaceutical Industry, Alan Morrison, Albert Wertheimer, 2002)(30)

1.1.3.1.2 Costs

There are several economic definitions of cost that apply. The most common definitions of costs used are the following:

Average cost: equivalent to the average cost per unit. It is the total cost divided the number of units or goods produced(34).

Direct cost: the cost of the goods and services that are used to provide a treatment. They can be borne by the healthcare system, community and patients' families in addressing the illness(34).

The direct costs in healthcare are divided in direct medical costs and direct non-medical costs (Direct Cost = Medical Costs + Direct Non-Medical Costs).

The direct medical costs are the costs payed for physician visits, drugs, hospitalizations, laboratory tests and medical supplies and equipment. The direct non-medical costs include a great number of various expenses from different origins, such as: transportation to health care facilities, special foods, etc.(30)

Fixed cost (overhead cost): the costs that remain, in a short time span, stable, regardless of the quantity produced, for instance: heating and lighting, insurance, providing space and administrative services, etc.(34)

Incremental cost: the increased cost of one treatment program relative to an alternative(34).

Indirect cost (productivity cost): the value of a productivity loss to society due to an illness. They are related to morbidity and derive from absenteeism (patients missing work), presenteeism (patients being less productive at work) and mortality costs (defined below)(30,34).

Indirect costs are then the sum of morbidity costs plus mortality costs (indirect costs = morbidity costs + mortality costs).

Intangible cost: the value of psychologic effects such as pain or suffering; costs that are impossible to quantify(30).

Marginal cost: costs that result from the production of an additional unit or service. It is relatively important to understand that marginal cost differs from incremental cost because incremental cost refers to treatment alternatives while the marginal cost refers to more of the same treatment(34).

Mortality cost: costs incurred due to death(34).

Avoided cost: costs avoided because of a healthcare intervention(34).

Opportunity cost: the value of all costs in a different course of action/alternative(30).

Production cost: total amount of resources needed to produce something(30).

After these definitions it is possible to conclude that total costs are the sum of direct costs plus indirect costs plus intangible costs(30):

Total Costs = Direct Costs + Indirect Costs + Intangible Costs

These definitions are useful to understand the methods and the results of the present study.

1.1.3.1.3 Perspective

Costs are seen differently from the different points of view of the stakeholders involved. In a CE analysis or in a cost-utility analysis the perspective refers to the vantage point of the analysis affecting the costs and the benefits relevant to the study itself. There are usually 4 perspectives possible: patient', provider's, payer's and societal perspective(35)(30).

Patient' perspective: costs in this perspective are essentially the one's the patient has to pay to benefit from a healthcare intervention. This perspective should be used when studying the effect of a certain program in the quality of life of the patients or the study of the indirect costs payed by the patient as "out-of-the-pocket" money(30).

Provider's perspective: in this perspective the costs represent the real costs of providing a service or product, regardless of what the provider charges. In this perspective, indirect costs are often not so important because they are, as well, not so important for the provider. This perspective of the healthcare organization should be adopted especially when making formulary management or drug-use policy decisions(30).

Payer's perspective: payers can be insurance companies, employers or the state (government). Most of the costs that matter to the payer are the direct costs, however indirect costs from absenteeism and presenteeism can also contribute to the total cost of healthcare in the perspective of the payer. Payer's perspective should be employed, for instance, when health care benefits are being selected for the employees of a certain company(30).

Societal perspective: it is the most extensive and broadest of all perspectives as it considers the costs and the benefits to society. In theory, every cost, direct or indirect, must be accounted for. In countries with where medicine is nationalized and, therefore, provided by the State, this is the most adequate perspective(30).

The authors of these analysis must cite clearly which is the perspective considered and the costs and benefits used have to be the ones relevant for the chosen perspective.

Moreover, for the reader, this is important to fully understand the study even on subject matter.

1.1.4 Modelling Frameworks: Markov Models and Influence Diagrams

Simple decision analysis models cannot describe diseases that progress gradually over time, sometimes, over a period of decades, while simultaneously the risk of the outcome of interest also increases with age. When presented with challenges like this, the appropriate approach is through Markov Models(36).

To understand these models that are a mix of influence diagrams and simple decision trees, first it is important to understand what are influence diagrams.

1.1.4.1 Influence Diagrams

Influence diagrams are diagrams used to help in the construction of more detailed decision trees. In this kind of diagrams, it is easy to understand the decision in discussion, the possible outcomes and the outcome of interest and the probability elements that influence the outcomes. Basically, it is possible to understand in a decision process which elements influence a decision process and the outcomes that emerge from this process(30). In the picture below, it is possible to see an example of an influence diagram:

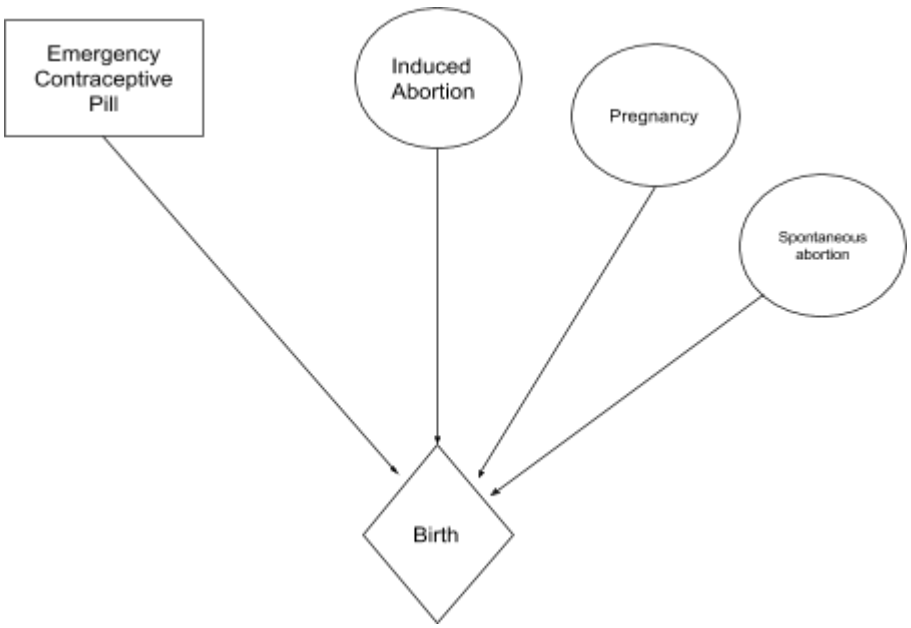


Figure 3 - Illustration of an influence diagram - the decision is showed in a square, the chance elements in circles and the outcome is presented in a lozenge shape (adapted from: Pharmacoeconomics: A Primer for the Pharmaceutical Industry, Alan Morrison, Albert Wertheimer, 2002) (30)**.**

1.1.4.2 Markov Models

Markov Models are very similar to simple decision analysis diagrams; however, the decision process is first mapped out in a Markov Diagram which is very similar to an influence diagram (see figure 326). In these diagrams there are various stages of disease (progressive) and different stages in times (cycles), where, at any given cycle, an individual must be in one of the stages of disease which include the stages: well and dead(30). In the next image an example of a Markov diagram can be seen:

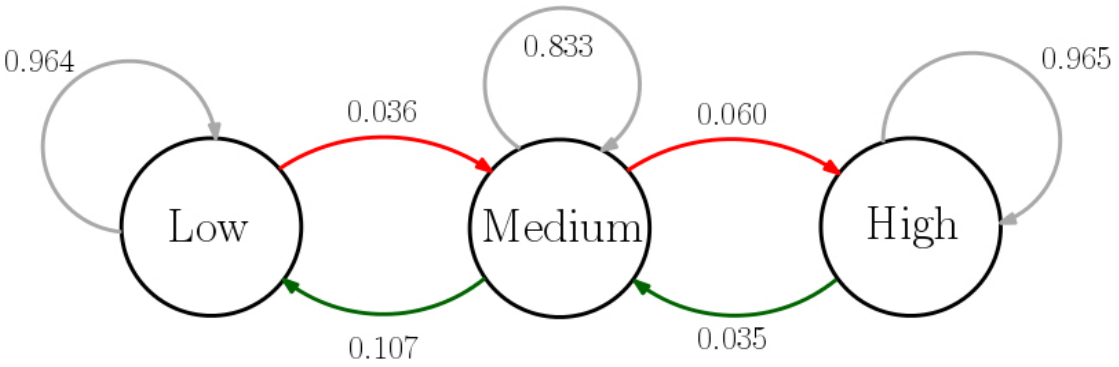


Figure 4 - A Markov Diagram for a risk of contagion: 3 stages can be seen denominated as "low", "medium" and "high". Both the transition probabilities and the possible pathways of the process are shown (adapted from: Exploring Risk Contagion Using Graph Theory and Markov Chains, Ken Deeley, 2007)(37)**.**

1.1.5 Clinical Epidemiology

In a pharmacoeconomic analysis both the cost input data as well as the effectiveness input data are needed. This makes epidemiological and medical research studies important tools in these data compilation. The studies used can be classified as observational or experimental, based on the interference of the investigator on the process. They can also be classified in prospective or retrospective, according to the time of occurrence of the events from which data is being generated. Last, the observations may refer to one point in time, being called cross-sectional, or to several points in time, being called longitudinal. Following this classification, the data used in the present study comes from clinical trials which can only be classified as prospective, longitudinal, experimental studies(31).

1.1.6 QALY, DALY and the Concept of Utility

In many healthcare related comparative studies, natural units like “number of patients that survived a specific intervention” are used, as well as indexes and ratios to express different, but comparable, health status(30).

To solve this problem some units like QALY (Quality-Adjusted Life Years), DALY (Disability-Adjusted Life Years) are frequently used though questioned by some authors.

In this kind of studies there’s the need of having units that turn different aspects, such as treatment options, protocols, interventions and technologies into comparable variables. To address this issue, units like the ones mentioned above were created.

1.1.6.1 The Concept of Utility

In health economics, an “utility” is a measure that represents the value that some individual attributes to a specific health state. It ranges from 0 (representing death) to 1 (representing perfect health). In the end, utilities reflect the strength of an individual’s preferences towards certain health-related outcomes.

Measuring health utilities is a complex process involving two steps: defining a set of health states of interest and valuing those states. There are direct and indirect ways of valuing those states. The methods of collecting data on utilities include: the standard gamble approach, the time trade-off approach and the visual analog approach. The main indirect methods are: the use of generic preference instruments (e.g. EQ-5D or HUI), the use of disease-specific measures and mapping from disease-specific-health-related quality of life instrument to a generic instrument. Note that some reference institutions like the NICE specify one method of preference (EuroQol: EQ-5D) for utility measurement in documents related to drug access decision-making(38).

Utilities are used to calculate QALYs as it will be explained in the next section and therefore are increasingly important in Pharmacoeconomics.

1.1.6.2 QALY

Created in the 1970s, the QALY (Quality-adjusted Life Year) is a unit that combines “the effects of health interventions on mortality and morbidity into a single index”(39). It is according to NICE (National Institute for Health and Care Excellence) “a measure of the state of health of a person or group in which the benefits in terms of length of life, are adjusted to reflect the quality of life”(40). QALYs can be calculated by multiplying the utility value associated with a given state of health by

the time lived in that state (in years). Therefore, one QALY represents 1 year of life in perfect health (1 year of life x 1 utility value) as opposed to one year with less health (state of health "χ", with χ <1) that values χ QALYs (1 year of life x χ = χ QALY)(41). The next figure shows the basic concept behind QALYs:

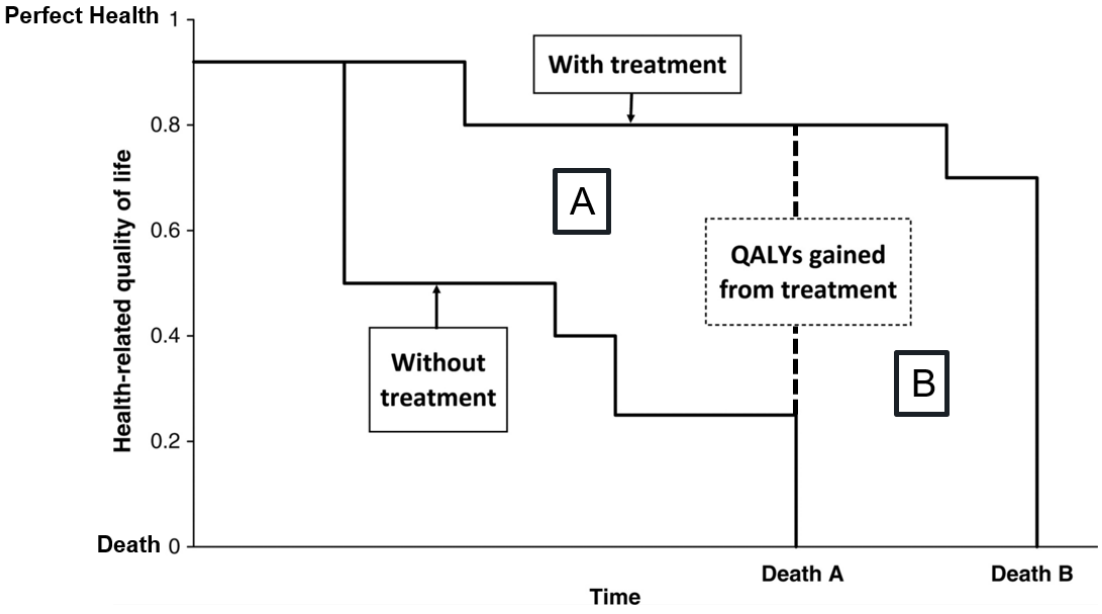


Figure 5 – The concept of the QALY (adapted from: Valuing life years: the concept of a QALY, Whitehead S., The British Medical Bulletin Volume 96, Issue 1, 2010)

In the figure, the QALYs gained by an individual submitted or not to a specific treatment/intervention are shown. Area "A" shows the benefits in quality of life mentioned above and area B shows the benefits in quantity of life for that individual when submitted to the treatment/intervention.

The area between the two curves (A+B) represents the QALYs gained by this individual from the treatment.

1.1.6.3 DALY

Disability-adjusted life years (DALY) is one of the most used alternative to QALY's among with Healthy Years Equivalent (HYE) and Willingness-to-pay (WTP).

DALYs were introduced in the 1990s with the purpose of serving as a summary measure of population health to estimate the global burden of illness. It is therefore considered an indicator of the relative impact of a specific illness or injury on losses in healthy life years. As in the QALY,

disability weights are applied to the time intervals with the disease and they are obtained recurring to a valuation exercise made with healthcare professionals(42).

There are two important differences between QALY and DALY. The first is that QALYs reflect the relative preferences of an individual or group for health states (hence their utilities) while DALYs reflect the degree to which health is reduced by a disease condition. The second is that DALY uses an age-weighting function that values years differently depending on the age of disease onset giving greater weight to a year lived by a young adult than a year lived by a child or elderly person(43).

The DALY is very used mostly for international comparisons of disease burden usually made by global organizations such as the WHO or the World Bank.

1.2 Warfarin, Novel Oral Anticoagulant Drugs and Atrial Fibrillation

Atrial Fibrillation (AF) affects 1-2% of the general population and prevalence is expected to double in the next 50 years. AF is nowadays linked directly to many cases of ischaemic stroke as it is one of its main causes. These strokes in patients with AF are usually very severe leading to numerous cases of profound disability or death(44).

The standard of care for ischaemic stroke prophylaxis in patients with AF is long-term anticoagulation provided by a vitamin K antagonist such as warfarin which is considered an effective treatment for stroke prophylaxis in AF patients. Because of its pharmacokinetics profile, routine monitoring of warfarin is made to ensure the correct anticoagulation effect is in place. This is measured using the International Normalised Ratio or INR being an INR of 2-3 considered optimum for patient suffering from nonvalvular AF(44).

Another important measure that allows valuating the quality of anticoagulation control is the percentage of time in therapeutic range (TTR). TTR can therefore be associated with the rate of some clinical events of relevance in these patients, such as ischaemic or haemorrhagic stroke.

Although these vitamin K antagonists such as warfarin are effective, they present themselves with the problem of having many drug-drug interactions and drug-food interactions making it very hard for patients and doctors to control in an optimal way the anticoagulation level and therefore leading more often to clinical episodes related to these issues.

Novel Oral Anticoagulant Drugs (NOACs) are a new alternative indicated for the prophylaxis of strokes in patients with AF. Opposite to warfarin, NOACs have much safer pharmacokinetic profiles, with smaller half-lives making them safer to use. This fact described before also affects

patient and clinicians in the way that no monitoring or dose adjustment is required. Still, some adverse events still occur, and it is important to state that of the three major NOACs: apixaban, dabigatran and rivaroxaban; only dabigatran has a specific antidote: idarucizumab which was approved by the Food and Drug Administration (FDA) in October 2015 and by European Medicines Agency (EMA) in November the same year(45).

The respective clinical trials: ARISTOTLE [Apixaban for Reduction in Stroke and other Thromboembolic Events in Atrial Fibrillation] for apixaban, (RE-LY [Randomized Evaluation of Long-Term Anticoagulation Therapy] for dabigatran and ROCKET-AF [Rivaroxaban Once-daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation] for rivaroxaban, demonstrated undoubtedly the efficacy and safety of NOACs when compared with dose-adjusted warfarin treatment(44).

As the outcomes of warfarin treatment rely heavily on factors such as the adequacy of the warfarin treatment, the quality of anticoagulation control achieved and possibly other factor external to the treatment such as the organization of the health system itself and the clinical protocols applied for each country a lot of studies were made to evaluate if in certain countries NOACs proved, or not, to be cost-effective alternatives to the standard warfarin treatment(46).

1.3 Aim of the Study

The aim of this study was to evaluate the difference in CE results obtained for five countries (Portugal, Slovenia, Sweden, The Netherlands and the United Kingdom (UK)) and to conclude on the differences and similarities between countries regarding sets of country-specific data applied to the same mathematical model. Particularly investigated sets of input data were drug costs, all costs (drug costs plus remaining clinical costs), utilities, mortality tables and other baseline characteristics (this last was not performed, detailed explanations on the reasons will be discussed further ahead). It is also relevant to define which NOAC is more CE in each country.

2 Materials and Methods

2.1 Materials

To reach the goals of the study, there was the need to find valid and consensual articles and publications on the CE of NOACs when used for AF in different countries. Also, there was the need to produce a very robust introduction to make sure that everyone could fully understand the subsequent parts of the study. To accomplish the goals stated before and for the base input data of the study, secondary bibliographic sources such as published articles were used. For the study itself a mathematical model was used along with TreeAgePRO software.

To further analyse the obtained data Microsoft Office solutions such as the EXCEL were used.

2.1.1 Secondary Sources

The secondary bibliographic sources used for this study were mainly published articles and books. Published articles used were searched using databases as the PubMed (United States National Library of Medicine) and through search engines as the Google Scholar and had to be as recent as possible. The keywords searched to retrieve the articles used to obtain data for the model were: CE; atrial fibrillation; NOAC; Novel Oral Anticoagulant Drug; Dabigatran; Rivaroxaban; Apixaban. The ones used to search for relevant information to the introduction are related to the reviewed topics.

In the introduction some information retrieved from websites was also used. The websites used were websites of valid and consensual credit, for instance the NICE (National Institute for Care and Health Excellence) website. Other websites, such as Wikipedia were not used as they are untrustworthy sources of information.

2.1.2 The Mathematical Model

The mathematical model used is based on the one designed by Andrej Janžič, PhD and Mitja Kos, PhD from the Chair of Social Pharmacy, Faculty of Pharmacy, University of Ljubljana, Slovenia described in the article: "Cost Effectiveness of Novel Oral Anticoagulants for Stroke Prevention in Atrial Fibrillation Depending on the Quality of Warfarin Anticoagulation Control." published in the journal “PharmacoEconomics” (April 2015 volume 33; issue 4; pages 395-408) (44). The researchers provided the full access to the model. Compared to the original one, two major changes were made: the high-dose edoxaban and the genotype-guided dosed warfarin branches of the

Markov Tree were suppressed because both were lacking available data in different countries that was necessary for conclusive comparisons. The picture below shows the Markov Tree used with the changes made:

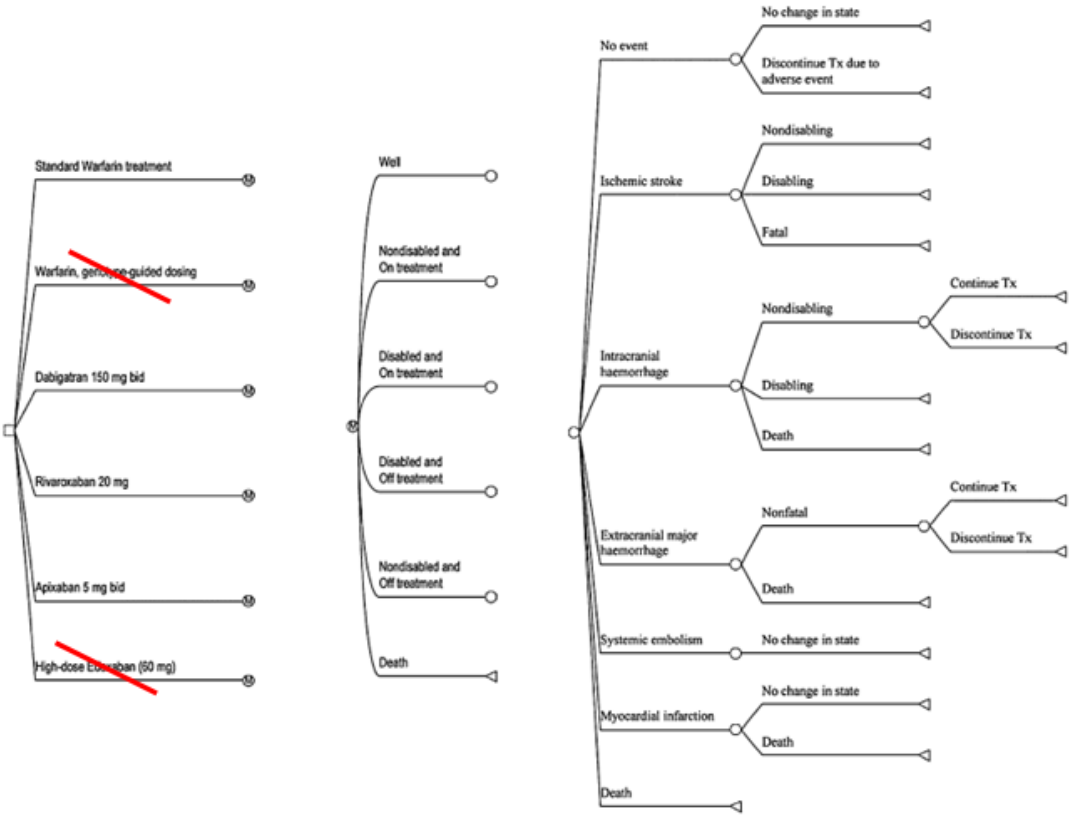


Figure 6 – Markov Tree used in this study (adapted from: Cost Effectiveness of Novel Oral Anticoagulants for Stroke Prevention in Atrial Fibrillation Depending on the Quality of Warfarin Anticoagulation Control, Andrej Janžič, Mitja Kos, 2014)(44)**.**

2.1.3 Microsoft Office Solutions: EXCEL

To further analyze the data generated by the TreeAgePRO software Microsoft EXCEL was used. The data from the simulations made by the TreeAgePRO software was exported to Microsoft EXCEL and a variety of tables were created to do more simulations on the software stated above. The Microsoft EXCEL was also used to generate the graphs needed to express the simulation results in a clearer and more reader-friendly way. The rationale used to generate data and conduct the study will be explained in the next section: “Methods”.

2.2 Methods

In this section the rationale used to conduct the study will be explained, as well as the reason why the countries selected were the ones mentioned in section 1.3.

The first step for this study was to select the countries to include in it. Above all the idea was to select countries that had published articles that had the data necessary to run the CE simulations on the TreeAgePRO software mentioned above but also make sure these were countries relevant either by their influence in healthcare, by the type of health system organization they presented or by the wide recognition they have in terms of CE studies and evaluations before important decisions on reimbursement, for instance, are made.

Out of several countries that met the criteria in terms of published articles, the selected were as mentioned before: Portugal, Slovenia, Sweden, The Netherlands and the United Kingdom (UK).

Portugal because it is my home country and because CE matters are increasingly becoming more and more important in the last few years after the austerity and the International Monetary Fund procedure in the country.

Slovenia as it was the country that helped me in the first place with this project but most of all because the mathematical model used was created in the first place for this country. This provides credibility to these data and allows for more conclusions on the validity of results and comparisons made.

Sweden as it has long been one of the European countries with biggest life expectancy which makes it a very good candidate to evaluate the influence of the mortality parameter on the results. Also, it is a country where CE Analysis is often used due to the strong Health Technology Assessment System for value based pricing.

The Netherlands was chosen as it is a country with a slightly different healthcare system compared to the others because not only has an insurance system but also has infrastructures that are specialized in certain kind of health care issues and that are widely recognized for certain services provided in a very narrow and specific area of intervention. As Sweden Health Technology Assessment is very important and common for value based pricing of medicines.

The UK was chosen because it is a country that allows access to a large variety of data, also has for some time a tradition in CE analysis and on its use for decision-making. It is also a country with a very acknowledged public healthcare system and regulator (NICE).

The title and authors of the articles mentioned above can be seen in the next table (table 2). As one can notice both The Netherlands and the United Kingdom had their data collected from the same article:

Table 2 – Date, Title and Authors of the articles used to retrieve most of the national specific data for the study.

Country	Title	Authors	Year	Reference
Portugal	"Cost-effectiveness of non-vitamin K antagonist oral anticoagulants for atrial fibrillation in Portugal"	João Costa et al.	2015	(47)
Slovenia	"Cost Effectiveness of Novel Oral Anticoagulants for Stroke Prevention in Atrial Fibrillation Depending on the Quality of Warfarin Anticoagulation Control"	Mitja Kos, Andrej Janžič	2014	(44)
Sweden	"Cost-effectiveness of Apixaban versus Warfarin and Aspirin in Sweden for Stroke Prevention in Patients with Atrial Fibrillation"	Tereza Lanitis et al.	2014	(48)
The Netherlands	"Cost Effectiveness of New Oral Anticoagulants for Stroke Prevention in Patients with Atrial Fibrillation in Two Different European Healthcare Setting"	Talitha I. Verhoef et al.	2014	(49)

United Kingdom	"Cost Effectiveness of New Oral Anticoagulants for Stroke Prevention in Patients with Atrial Fibrillation in Two Different European Healthcare Setting"	Talitha I. Verhoef et al.	2014	(49)

With these articles it was possible to gather a great proportion of the data needed to run the simulations with the software and mathematical model already explained in the sections above.

It is also important to state the dosage of the Novel Oral Anticoagulant Drugs used for this study: Apixaban 5mg; Dabigatran 150mg; Rivaroxaban 20mg.

For the reader's comfort and to facilitate the work during the study, all the input data for the 5 countries was compiled in Model Input Tables. These included all the variables and corresponding data for the study. These can have some adjustments depending on the country and are shown along with the corresponding values as attachments of this study (attachments A1.1 to A5.3).

The articles provided the major part of the data needed to fill the National Specific Model Input Tables. The mortality tables also needed for the study were gathered from following sources and refers to the following period (table 5):

Table 3 – Source, Period and Date of Mortality Tables used in the present study.

Country	Source	Period	Date
Portugal	Instituto Nacional de Estatística	2013-2015	27th May 2016
Slovenia	Republika Slovenjia Statistični Urad	2007	2008
Sweden	Statistiska Centralbyrån	2011-2015	29th November 2016
The Netherlands	SPO, Den Haag	2005-2010	February 2014
United Kingdom	Office for National Statistics	2013-2015	27th September 2017

All the compiled data was ready to be used in the software to run the mathematical model simulations on CE. The simulations were made to better understand the changes between the different countries and what variables among the ones showed before would have a bigger influence on the overall CE result for each drug and country. For that 7 types of simulation for each country were created. They are described below:

1 - Drug Cost (DC)

All the data used on this type of simulation was collected from the original input table of the Slovenian published article except for the drug costs that were those specific to each country. Note that for Sweden only Warfarin and Apixaban were considered due to lack of data on the other two: Rivaroxaban and Dabigatran.

2 - All Costs (Drug Costs + All Other Cost Variables) (ALLC)

All the data used on this type of simulation was collected from the original input table of the Slovenian published article except for the drug costs and all other cost variables including event costs the costs used were specific to each country. Note that for Sweden only Warfarin and Apixaban were considered due to lack of data on the other two: Rivaroxaban and Dabigatran.

3 - All Utilities (ALLUT)

All the data used on this type of simulation was collected from the original input table of the Slovenian published article except for the utilities that in this case the specific values for each country were used.

4 - Mortality Tables (MT)

All the data used on this type of simulation was collected from the original input table of the Slovenian published article except for the mortality tables. In this case the mortality tables of each different country were used in the simulations.

5 - Other Baseline Characteristics (OBC)

This type included the baseline characteristics that were specific to the model used and therefore were collected from the original input table of the Slovenian published article for every country. As

they were the same, the simulations of this type were not performed as they were going to have the same results and therefore have no influence or interest in the light of this study.

6 - National Adopted Model (NAM)

This type of simulation named National Adopted Model included all the costs specific to each country plus the mortality tables for the respective country. This simulation therefore reflects the changes made by these two variables together: all the costs plus the mortality tables. By maintaining the utilities from the original Slovenian article, it is possible to conclude on the effects of both costs and mortality tables of each country on the overall cost effectiveness.

7 - National Adopted Model + Utilities (NAM+UT)

This is the final type of simulation made and includes all the data from each country: all costs, mortality tables, and of course the utilities described in each article of each country. It represents the final CE analysis for each drug in each country. It is with this final type of simulation that overall conclusions can be made and discussed.

The next schematic clarifies the way the study was conducted. As it can be clearly understood it was conducted in a way that allows to understand what variables have most effect on the result as well as how will they affect it.

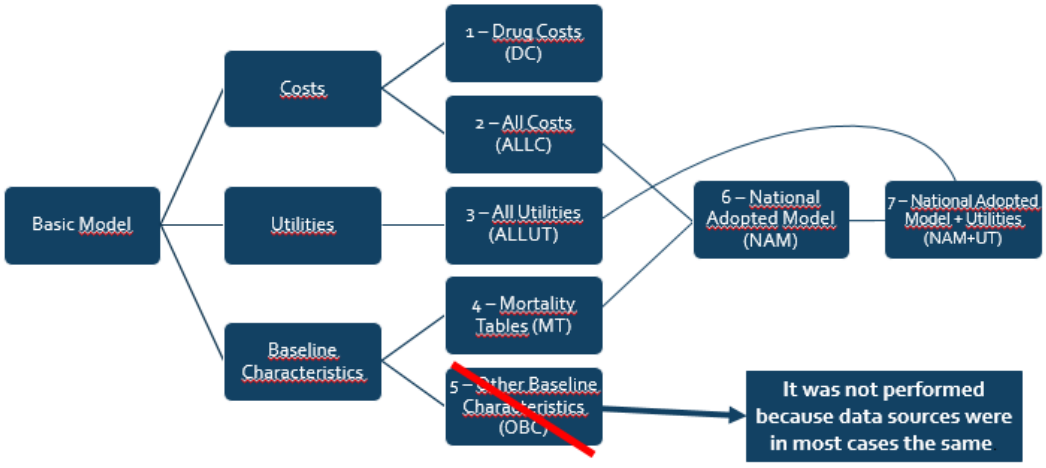


Figure 7 – Schematization of the simulations made in this study.

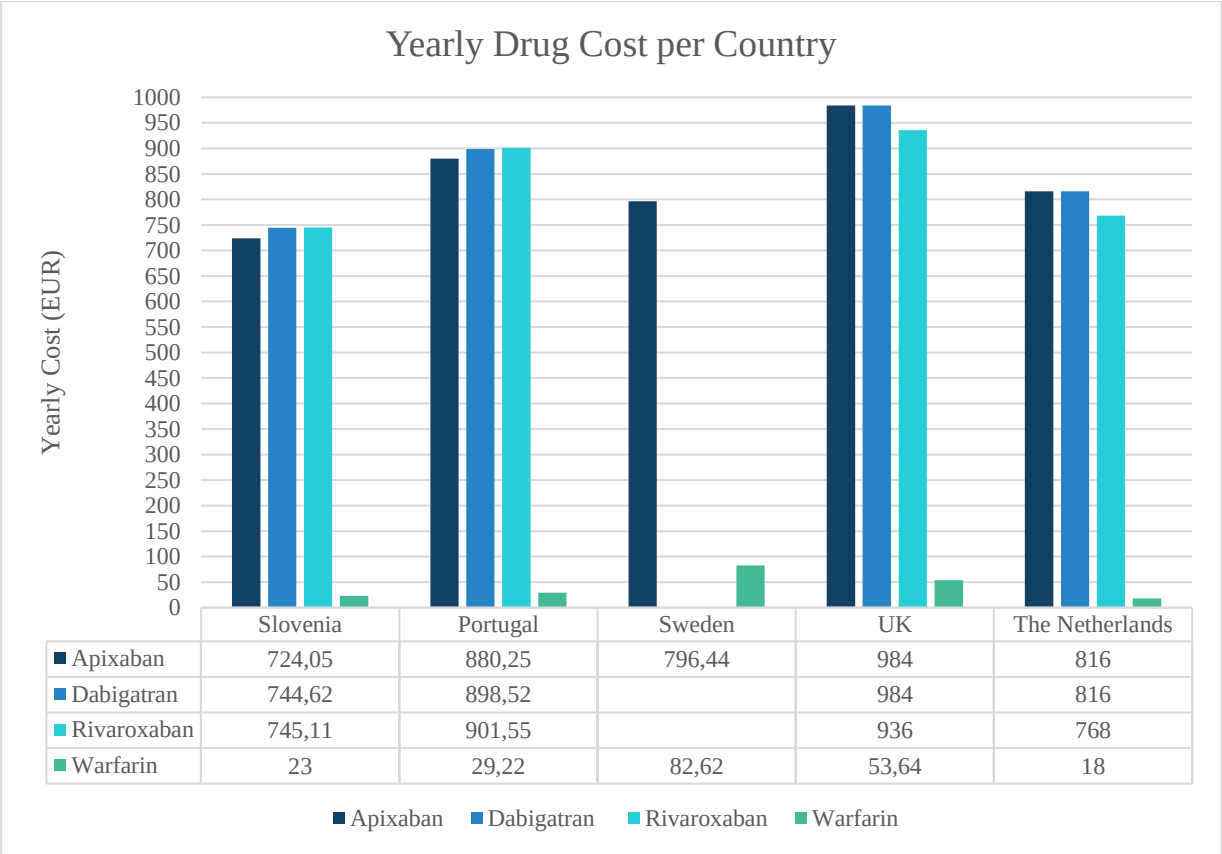
After performing all the simulations of each type referring to each country it was possible to analyse the results by exporting them to EXCEL and creating the CE graphs as well as simulated cost outcomes for each variable or simulated effectiveness outcomes. The results can be seen next in the results and discussion section.

3 Results and Discussion

After performing the simulations, CE graphs for each country were obtained. In this section these graphs will be analysed and discussed along with the simulated cost outcomes and simulated effectiveness outcomes for the variables themselves. It is possible with the latter two to understand how the variables tested such as drug cost, event cost, mortality tables and utilities influence and affect the result of the overall CE graph of each country. The comparison between these and the final ones allows a better understanding of how the result of CE is shaped country.

3.1 Drug Costs

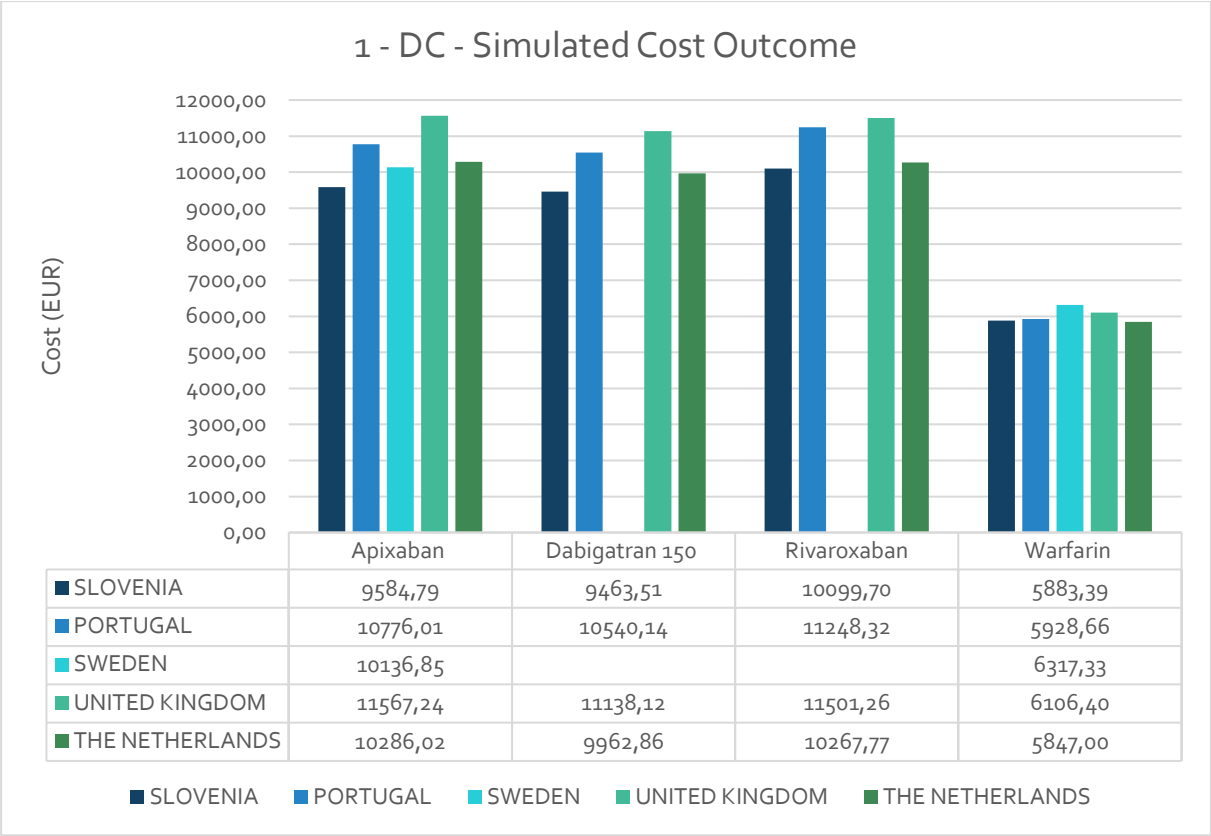
The first variable to analyse is the drug costs. The drug cost analysed is the Yearly Drug Cost. This varies a lot between the countries mentioned in this study. Warfarin as expected is the cheapest in all 5 countries. Nonetheless, the Yearly Cost of Warfarin also varies between the countries with Sweden having a cost for Warfarin that is substantially higher than any of the other countries. Rivaroxaban is the most expensive both in Slovenia and in Portugal while in the UK and in The Netherlands Apixaban and Dabigatran have the same Yearly Cost and are both the more expensive option. It is also interesting that in Portugal and Slovenia Apixaban is the cheaper drug yearly besides Warfarin. Another important consideration is that the Yearly Cost of Warfarin in The Netherlands is the lowest among the countries which was at first glance unexpected. All the Yearly Costs discussed above can be clearly seen in the next figure:



	Slovenia	Portugal	Sweden	UK	The Netherlands
Apixaban	724,05	880,25	796,44	984	816
Dabigatran	744,62	898,52		984	816
Rivaroxaban	745,11	901,55		936	768
Warfarin	23	29,22	82,62	53,64	18

Figure 8 – Data Comparison, Yearly Drug Cost of Warfarin, Apixaban, Dabigatran and Rivaroxaban.

After comparing the costs, the first cost outcome simulation, in which every data used on the model was from the original Slovenian article (44) except for the drug costs, was run. The results reflect largely the Yearly Cost of the Drugs seen before. Even though some of the biggest differences in costs are closed when adding all the remaining data and performing the analysis, this is particularly easy to see in the case of Warfarin in Sweden despite still being the country with higher outcome cost for Warfarin. It is also visible that Apixaban has higher outcome costs than Dabigatran, only surpassed by Rivaroxaban. These changes can be seen in the next figure:

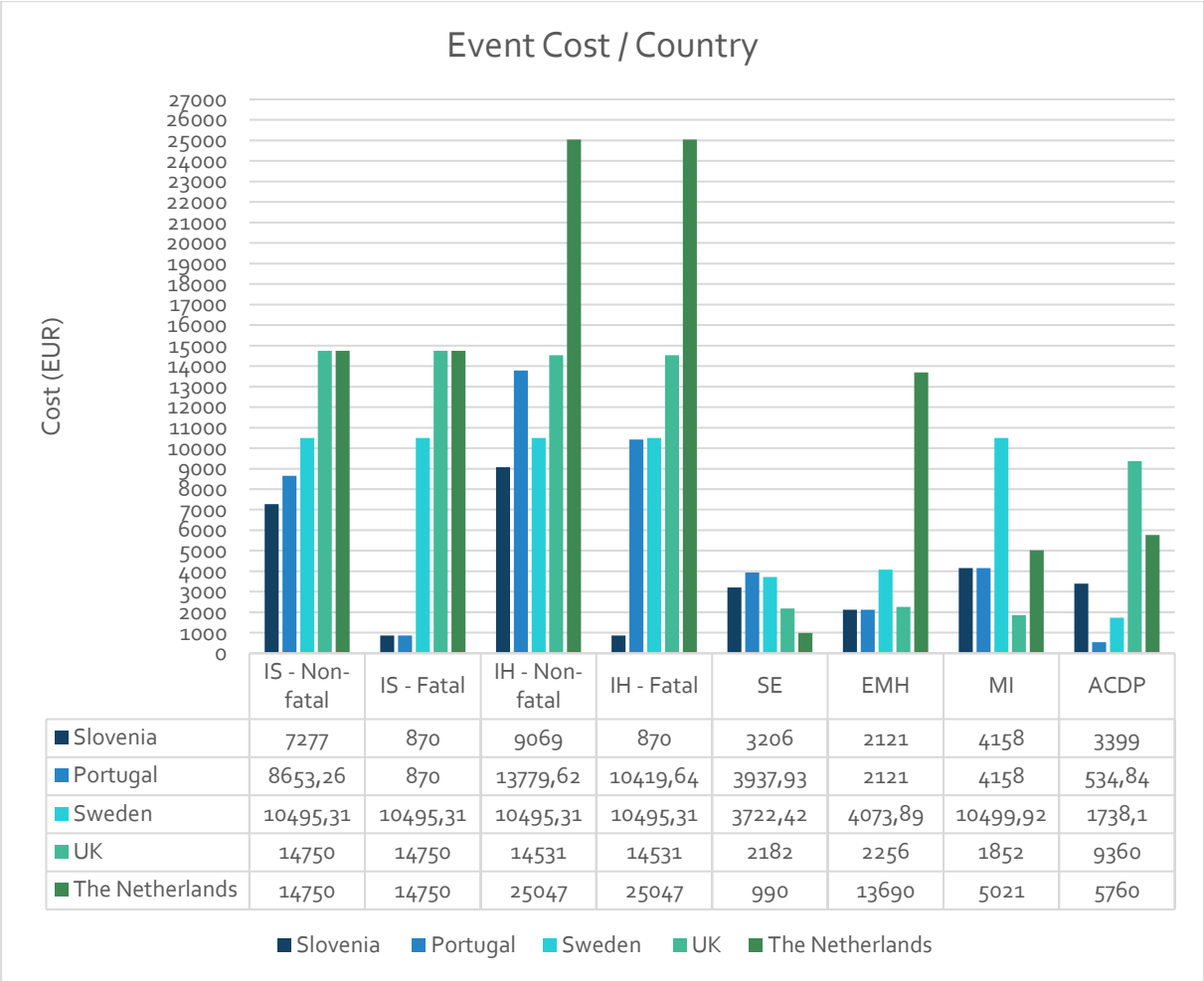


	Apixaban	Dabigatran 150	Rivaroxaban	Warfarin
SLOVENIA	9584,79	9463,51	10099,70	5883,39
PORTUGAL	10776,01	10540,14	11248,32	5928,66
SWEDEN	10136,85			6317,33
UNITED KINGDOM	11567,24	11138,12	11501,26	6106,40
THE NETHERLANDS	10286,02	9962,86	10267,77	5847,00

Figure 9 – Simulated Cost Outcome (1 - Drug Cost)

3.2 All Costs (Event Costs + Drug Costs)

For the second outcome cost simulation, event cost was introduced in the model. This means that in this second performed simulation both the drug cost and the event cost were changed from the original ones in the Slovenian article (44) to the specific ones for each country. Before comparing the simulated outcome cost for this variable (2 - All Costs (ALLC)), it is interesting to compare the cost of each event by country. These are shown in the next figure:



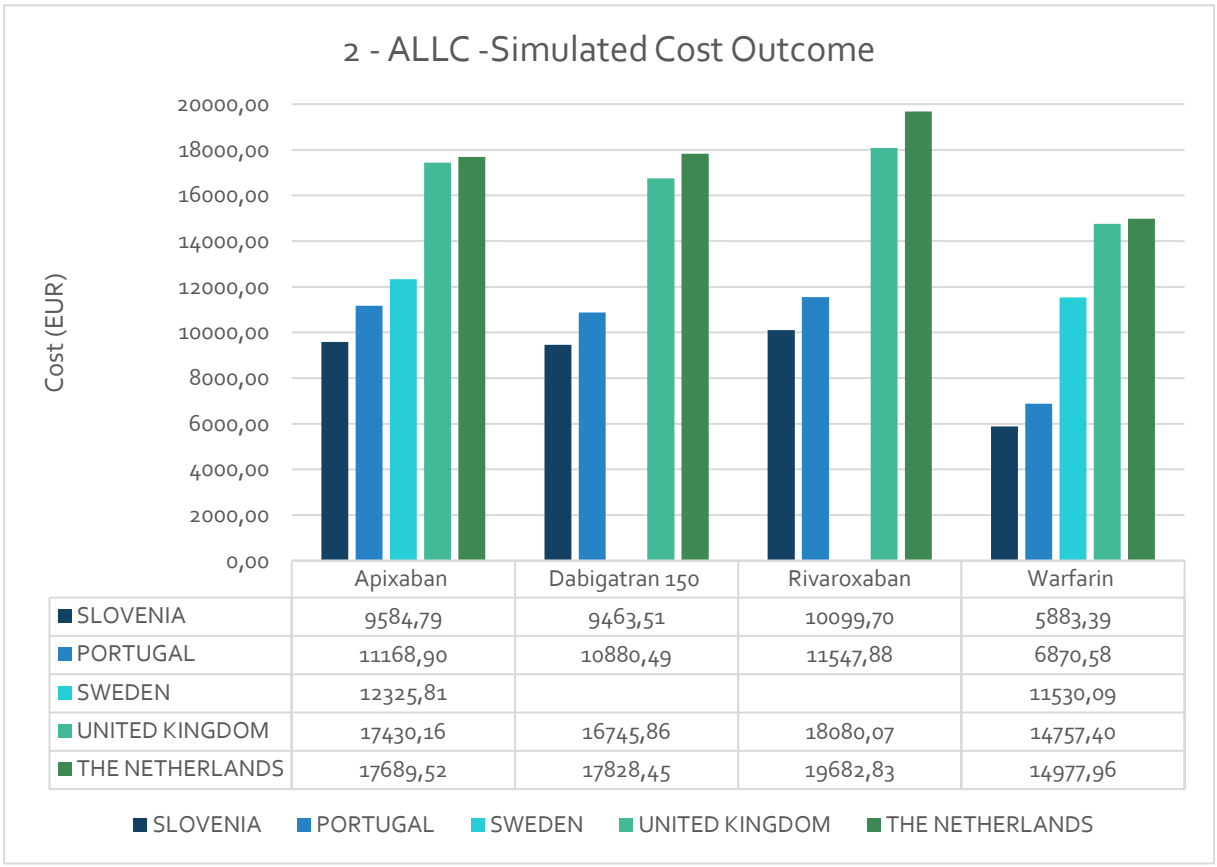
	IS - Non-fatal	IS - Fatal	IH - Non-fatal	IH - Fatal	SE	EMH	MI	ACDP
Slovenia	7277	870	9069	870	3206	2121	4158	3399
Portugal	8653,26	870	13779,62	10419,64	3937,93	2121	4158	534,84
Sweden	10495,31	10495,31	10495,31	10495,31	3722,42	4073,89	10499,92	1738,1
UK	14750	14750	14531	14531	2182	2256	1852	9360
The Netherlands	14750	14750	25047	25047	990	13690	5021	5760

Figure 10 – Event Cost per Country: IS – Ischaemic Stroke; IH – Intracranial Haemorrhage; SE – Systemic Embolism; EMH – Extracranial Major Haemorrhage; MI – Myocardial Infarction; ACDP - Annual Cost for Disabled Patients;

It is possible already to see that The Netherlands have the highest event cost followed by the UK and that is visible mostly on the more important clinical events (the ones with more probability of occurring in cases of AF), such as Ischaemic Stroke or Intracranial Haemorrhage. Also, even though Sweden is regarded as an expensive country the cost of events are still comparable with the Portuguese setting, being Slovenia the country where the costs are lower. Note that in the Netherlands and in the UK no difference is made between fatal and non-fatal events and that both have the same cost for IS. It is also interesting that Sweden has the bigger event cost for Myocardial Infarction which stands out from the rest of the event costs in this country. The differences in these costs have to do with medical and clinical protocols specific from each country as well as with the way the healthcare system is organized. This is important to understand the surprising differences between countries for the same kind of clinical events.

Then the simulated cost outcome graph was obtained, and it is easy to understand from the data that event cost has a bigger influence on the cost-outcome result than the price of medicines itself. In this second simulation a gap between two groups of countries starts to appear: on one side Portugal and Slovenia and on the other the UK and The Netherlands being Sweden in the middle in terms of outcome costs. Also, all the costs after this simulation have risen somewhere around 10000€ compared to the simulation where only drug costs were included. This proves that the event costs have a bigger influence on the overall cost outcome result, and predicts that event costs will have a very big influence in the CE result.

Regarding the medicines, it is important to state that Rivaroxaban treatment presents the higher outcome cost and Warfarin the cheaper. Even tough, the gap between the cost of using Warfarin or the NOACs is minimized when event costs are put in the equation. It is also important to consider that the outcome cost of Warfarin in the UK and in The Netherlands, is higher when event costs are introduced in the model, than the outcome cost of every other NOAC in Portugal and Slovenia and of Apixaban in Sweden. The cost outcome graph can be seen next:



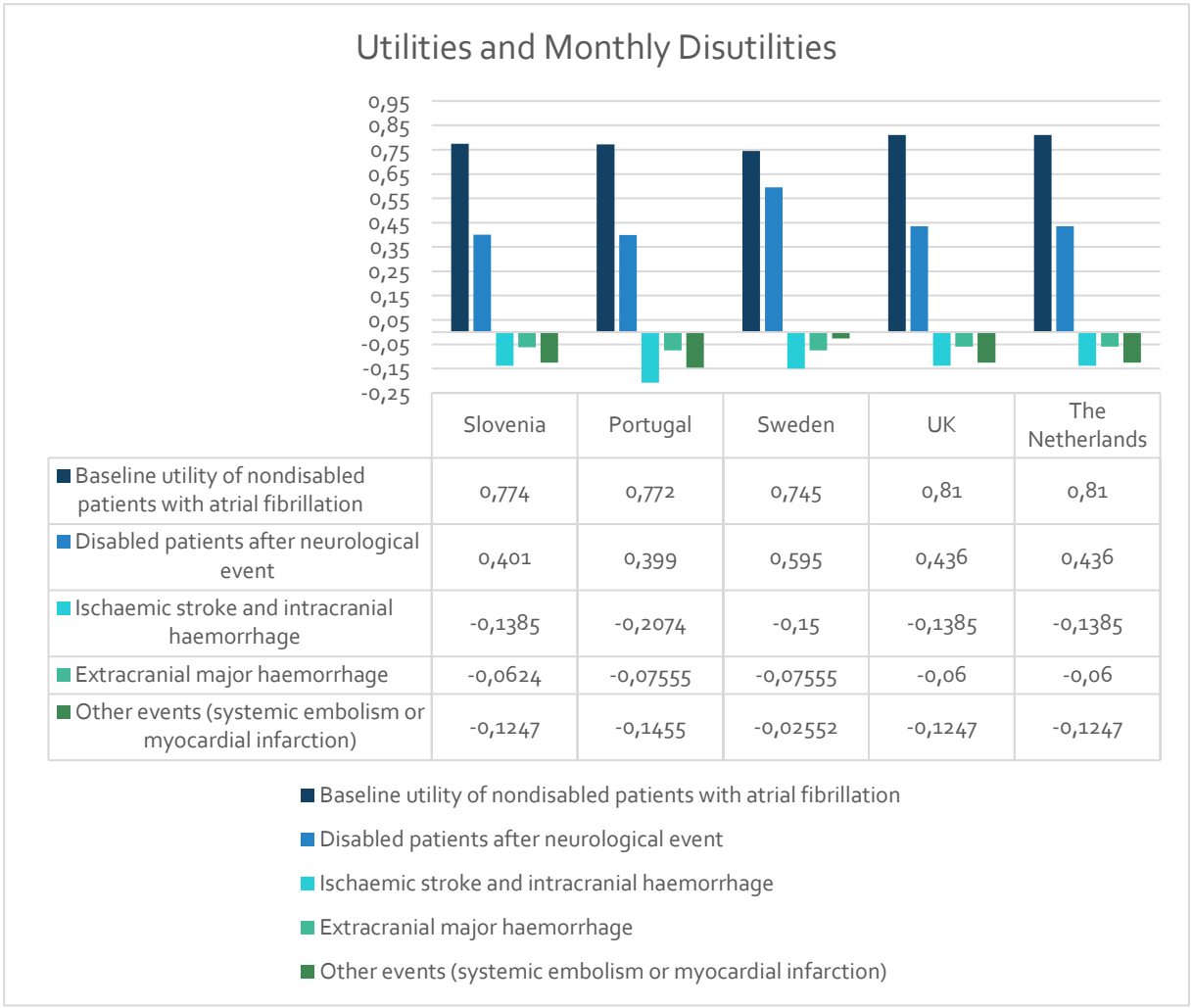
	Apixaban	Dabigatran 150	Rivaroxaban	Warfarin
SLOVENIA	9584,79	9463,51	10099,70	5883,39
PORTUGAL	11168,90	10880,49	11547,88	6870,58
SWEDEN	12325,81			11530,09
UNITED KINGDOM	17430,16	16745,86	18080,07	14757,40
THE NETHERLANDS	17689,52	17828,45	19682,83	14977,96

Figure 11 – Simulated Cost Outcome (All Costs – ALLC) – Includes drug costs plus event costs.

Concluding on the Cost Outcome analysis showed before it is possible to say that that Event Costs have a very important role and therefore, will also have on the final CE analysis being one of the key factors.

3.3 All Utilities

In the third simulation the effectiveness outcome was obtained changing only the utilities and monthly disutilities in the model to match the ones from each country. In the next figure these can be compared between countries:

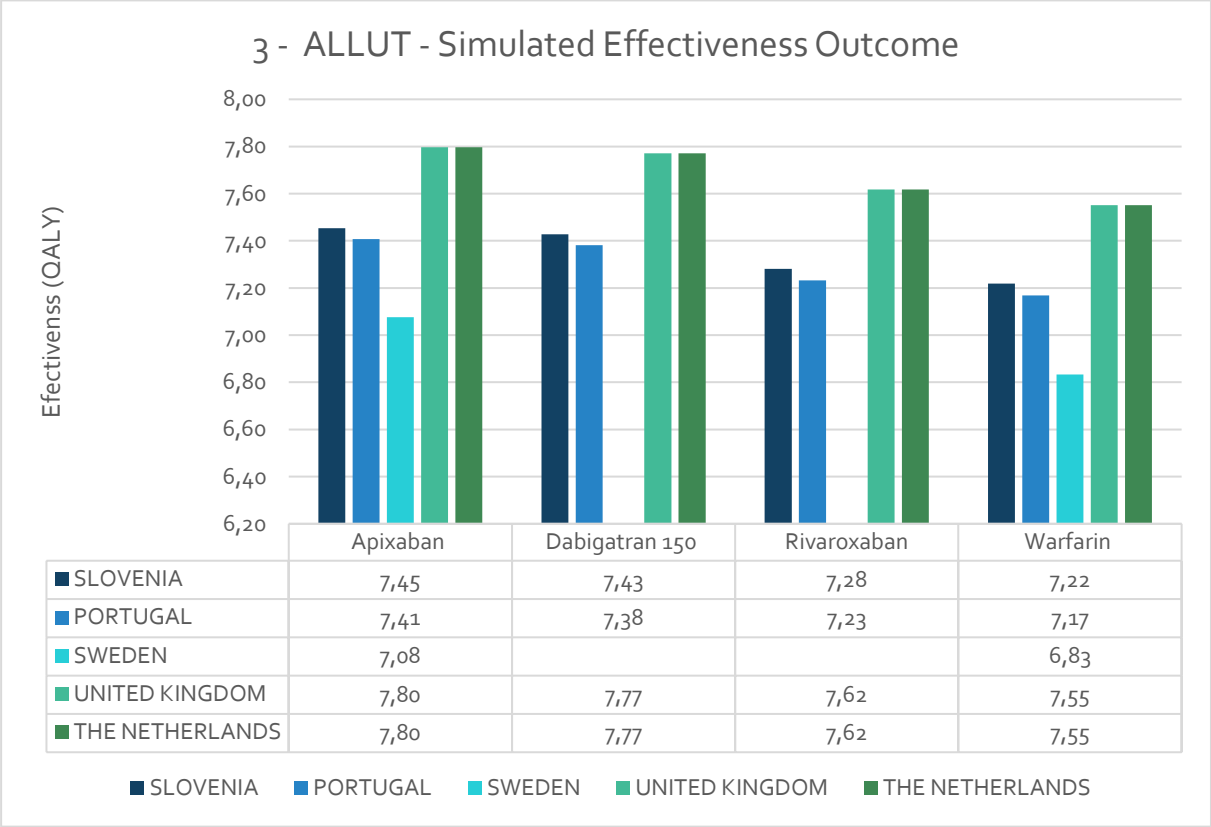


	Slovenia	Portugal	Sweden	UK	The Netherlands
Baseline utility of nondisabled patients with atrial fibrillation	0,774	0,772	0,745	0,81	0,81
Disabled patients after neurological event	0,401	0,399	0,595	0,436	0,436
Ischaemic stroke and intracranial haemorrhage	-0,1385	-0,2074	-0,15	-0,1385	-0,1385
Extracranial major haemorrhage	-0,0624	-0,07555	-0,07555	-0,06	-0,06
Other events (systemic embolism or myocardial infarction)	-0,1247	-0,1455	-0,02552	-0,1247	-0,1247

Figure 12 – Utilities and Monthly Disutilities per Country.

The utility and monthly disutility values have only slight changes. Both the baseline utility of non-disabled patients with AF and the one for disabled patients after neurological event have small numerical differences between countries but present the possibility of causing relevant changes in the simulated effectiveness outcome due to the importance of these two in the mathematical model. Note that in this third simulation Slovenia will act as a default case because the Slovenian data will be used for every country except in the case of utilities and monthly disutilities.

In the next figure the simulated effectiveness outcome is shown:



	Apixaban	Dabigatran 150	Rivaroxaban	Warfarin
SLOVENIA	7,45	7,43	7,28	7,22
PORTUGAL	7,41	7,38	7,23	7,17
SWEDEN	7,08			6,83
UNITED KINGDOM	7,80	7,77	7,62	7,55
THE NETHERLANDS	7,80	7,77	7,62	7,55

Figure 13 – Simulated Effectiveness Outcome (3 – All Utilities - ALLUT).

Using only the specific data correspondent to utilities and monthly disutilities both The Netherlands and the UK have the higher effectiveness outcomes (in QALY) for every drug. Note that the UK and the Netherlands share the same input parameters in the case of utilities and disutilities and therefore have the same result in this simulation (this happens because the original data was retrieved for both countries from the same article and in it these parameters were considered the same).

Apixaban shows the best results when it comes to effectiveness in this third setting in all the 5 countries. Dabigatran comes seconds in terms of effectiveness when only changing utilities and disutilities.

Rivaroxaban, surprisingly, comes very close to the Warfarin effectiveness levels in this simulation. In terms of QALY it is actually closer to Warfarin in all 5 countries than to the other NOACs.

3.4 Mortality Tables

In the fourth simulation the mortality tables were changed to the ones corresponding to each country. The rest of the data used in the model was from the Slovenian original article (44). This makes it easier to understand the impact of the mortality tables in the CE analysis.

At first the life tables of each country were put into the same graph to compare the probability of death at each age for each country. The results are shown in the next figure:

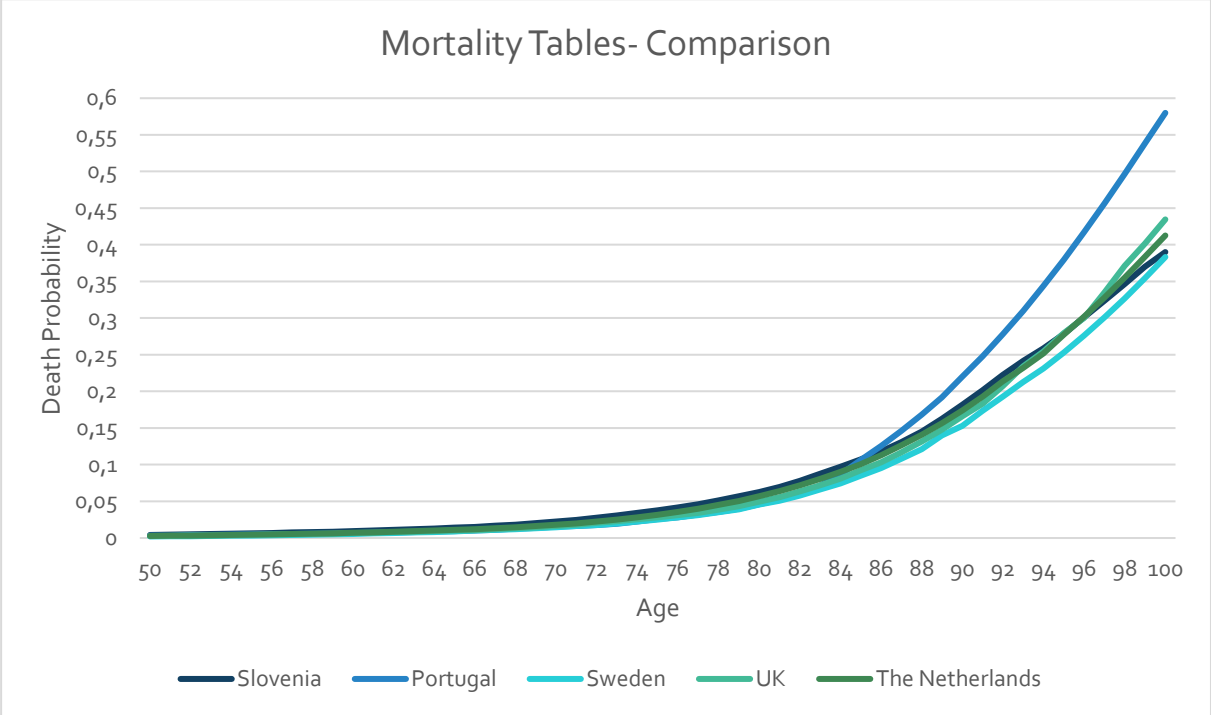


Figure 14 – Mortality Tables – Comparison between countries from the ages of 50 to 100-years-old.

This comparison shows that Portugal as the highest death probability for individuals over 85-years-old and that Sweden has the lowest death probability for individuals with the same age.

At first glance it was then expected that when introducing these data in the model, Portugal would have the lowest effectiveness outcome compared to the others and Sweden the highest one.

This would be true, if the model wouldn't consider mostly the ages between 70 and 85- years-old since patients enter the model at 70 years-old and simulated survival is set around 10-15 years. When we render the previous graph just with ages between 70 and 90-years-old (figure 15) we can clearly see that Portugal, alongside Sweden, has the lowest death probability at those ages which explains the simulated effectiveness outcome results seen in figure 16.

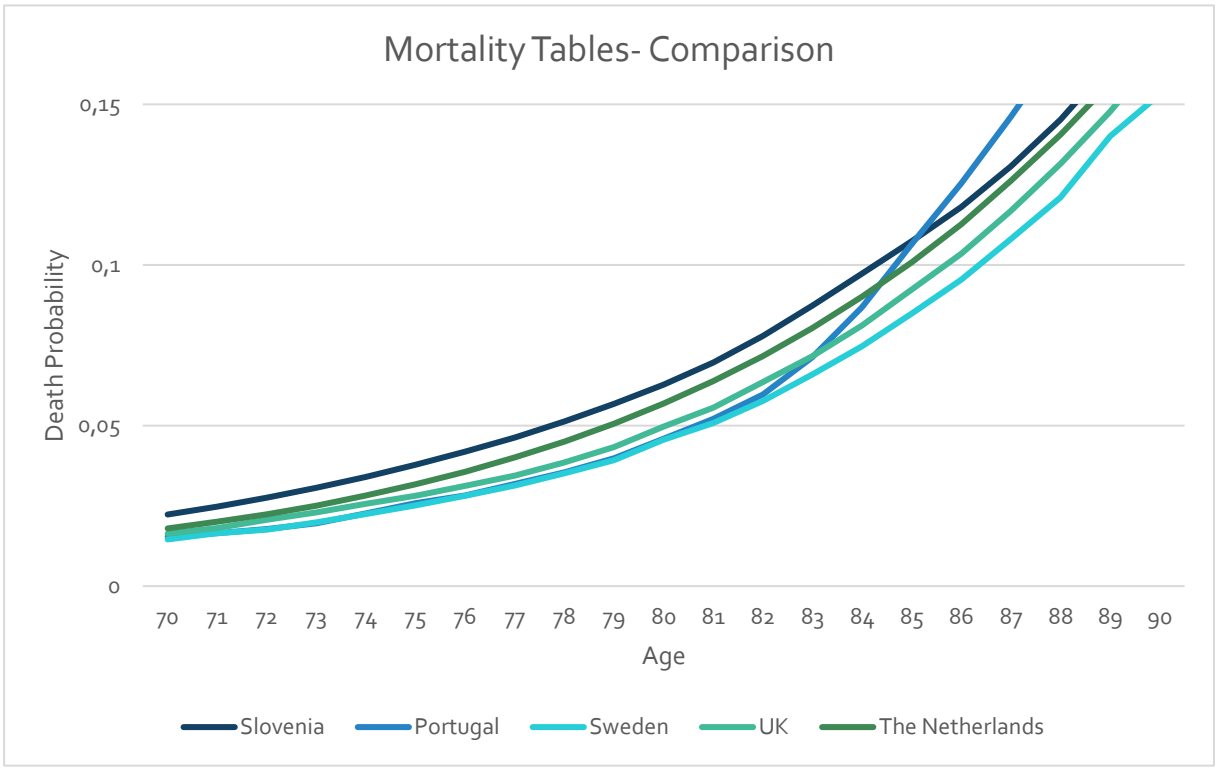


Figure 15 – Mortality Tables – Comparison between Countries from the ages of 70 until 90-years-old.

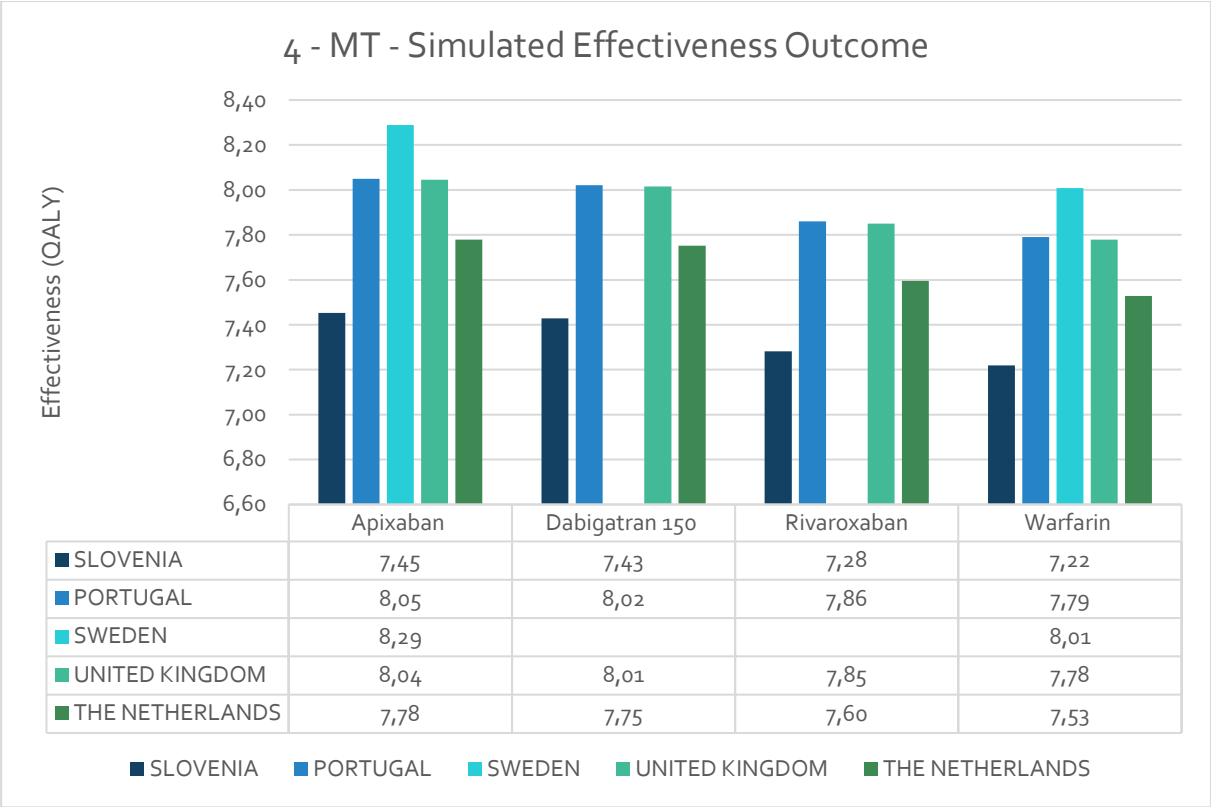
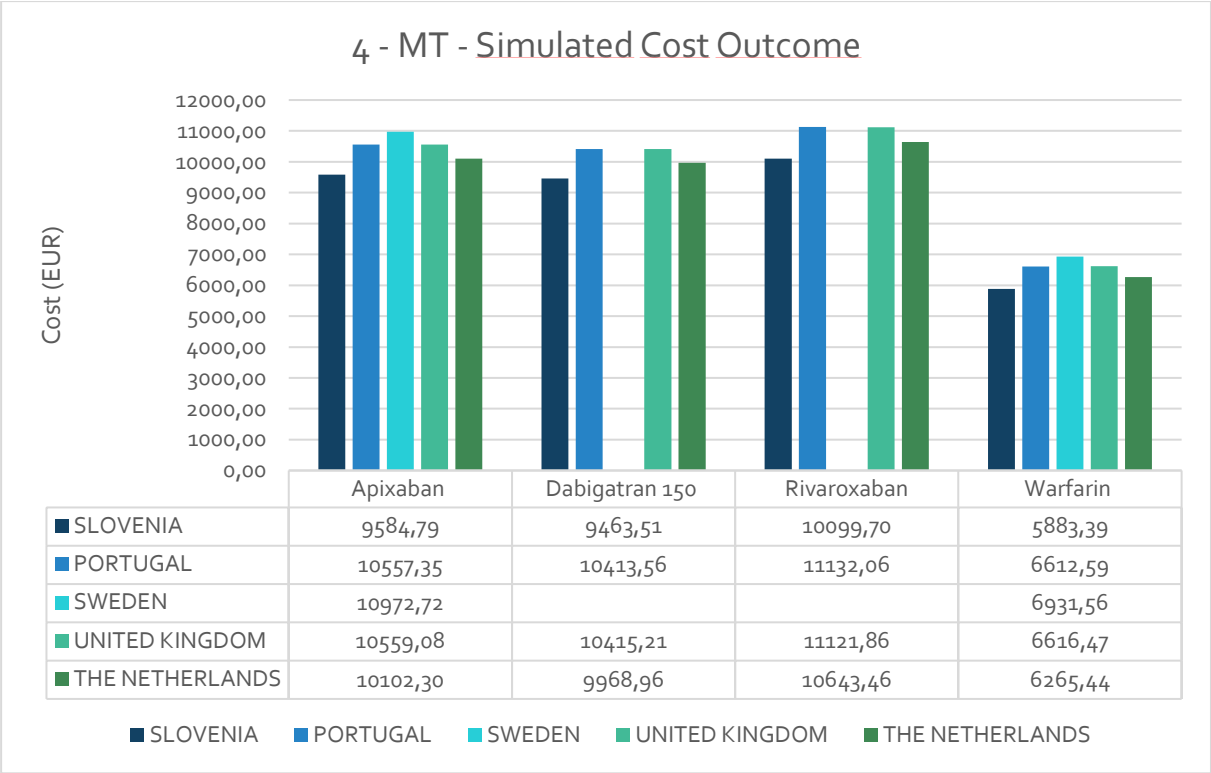


Figure 16 – Simulated Effectiveness Outcome (4 – Mortality Tables - MT).

In figure 16, Portugal shows effectiveness outcomes comparable to the ones of the UK, showing higher effectiveness outcomes in QALYS than The Netherlands, for instance. Again, Apixaban is the more effective of the 3 NOACs in these 5 countries and Rivaroxaban yet again shows little improvement in QALY when compared to Warfarin, this of course when only introducing national-specific mortality tables and using Slovenian values to fill the rest of the data needed to run the simulations.

As one can expect, the introduction of national-specific life tables in the model, also affects the simulated cost outcome. The impact though is low, and naturally, the countries with lower death probability rates present higher cost outcomes when compared to the reference, which is Slovenia. This can be seen in the next figure:



	Apixaban	Dabigatran 150	Rivaroxaban	Warfarin
SLOVENIA	9584,79	9463,51	10099,70	5883,39
PORTUGAL	10557,35	10413,56	11132,06	6612,59
SWEDEN	10972,72			6931,56
UNITED KINGDOM	10559,08	10415,21	11121,86	6616,47
THE NETHERLANDS	10102,30	9968,96	10643,46	6265,44

Figure 17 – Simulated Cost Outcome (4 – Mortality Tables - MT).

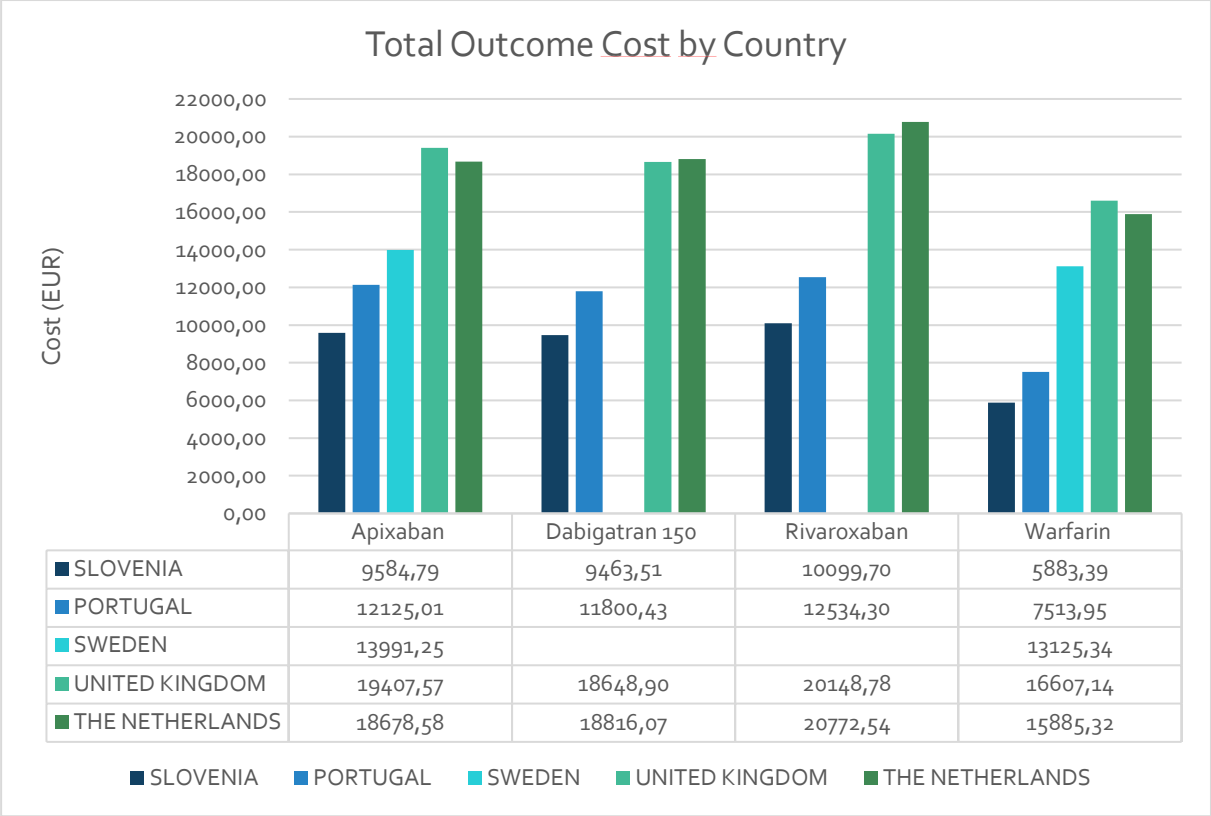
Even in this simulation, Rivaroxaban has the higher cost outcome of the three NOAC.

3.5 National Adopted Model, Total Outcome Cost by Country

In the next simulation, where all the costs specific to each country plus the mortality tables for the respective country were introduced (6 – National Adopted Model – NAM) we have the Total Outcome Cost by Country, since only the national specific utilities are still left to introduce in the model.

The results of this simulation prove that when combining all the data that affect the cost outcome, the two groups of countries mentioned above: Slovenia and Portugal to one side (lower cost outcomes) and The Netherlands and the UK to the other (higher cost outcomes). This also confirms Rivaroxaban as the more expensive option in terms of cost outcomes, and Warfarin as the cheapest.

It is also interesting to see that Warfarin in Sweden, the UK and the Netherlands has a higher outcome cost than Dabigatran and Apixaban in Portugal and Slovenia which shows the clear differences and impact the national specific data can have on the cost outcome results of a treatment with a specific drug in different countries. These results can be seen in the next figure:



	Apixaban	Dabigatran 150	Rivaroxaban	Warfarin
SLOVENIA	9584,79	9463,51	10099,70	5883,39
PORTUGAL	12125,01	11800,43	12534,30	7513,95
SWEDEN	13991,25			13125,34
UNITED KINGDOM	19407,57	18648,90	20148,78	16607,14
THE NETHERLANDS	18678,58	18816,07	20772,54	15885,32

Figure 18 – Total Outcome Cost by Country (6 – National Adopted Model – NAM).

When analysing all the variables that have an impact in the Total Cost Outcome by Country it is possible to conclude that Event Costs affect in a much bigger proportion the results than Mortality Tables. In the second simulation (2 – ALLC) where both drug cost and event cost were introduced we concluded that event costs had a much bigger impact than the drug costs itself. Now comparing the results with the ones from the fourth cost outcome simulation (4 – MT) we can clearly state that the Event Costs have a major impact in the Total Outcome Costs. These in proved by the similar result they both present:

Figure 19 – The impact of Event Costs and of the Mortality Tables in the Total Cost Outcome by Country.

3.6 National Adopted Model + Utilities, Effectiveness Outcome by Country

In the last type of simulation ran, all the data introduced in the model was specific to each country as seen in attachments A1.1 to A5.3. By adding the utilities of each country to the model it is finally possible to obtain the overall CE graphs of each country. Transforming the CE scatter graph in a bar graph (as it was made in all the previous simulations) helps comparing the effectiveness of each NOAC in all 5 countries when submitted to the same Markov Tree in the Software.

The overall CE graphs for the 5 countries can be seen in figures 20 to 24 and the bar graph mentioned above can be seen next in figure 25:

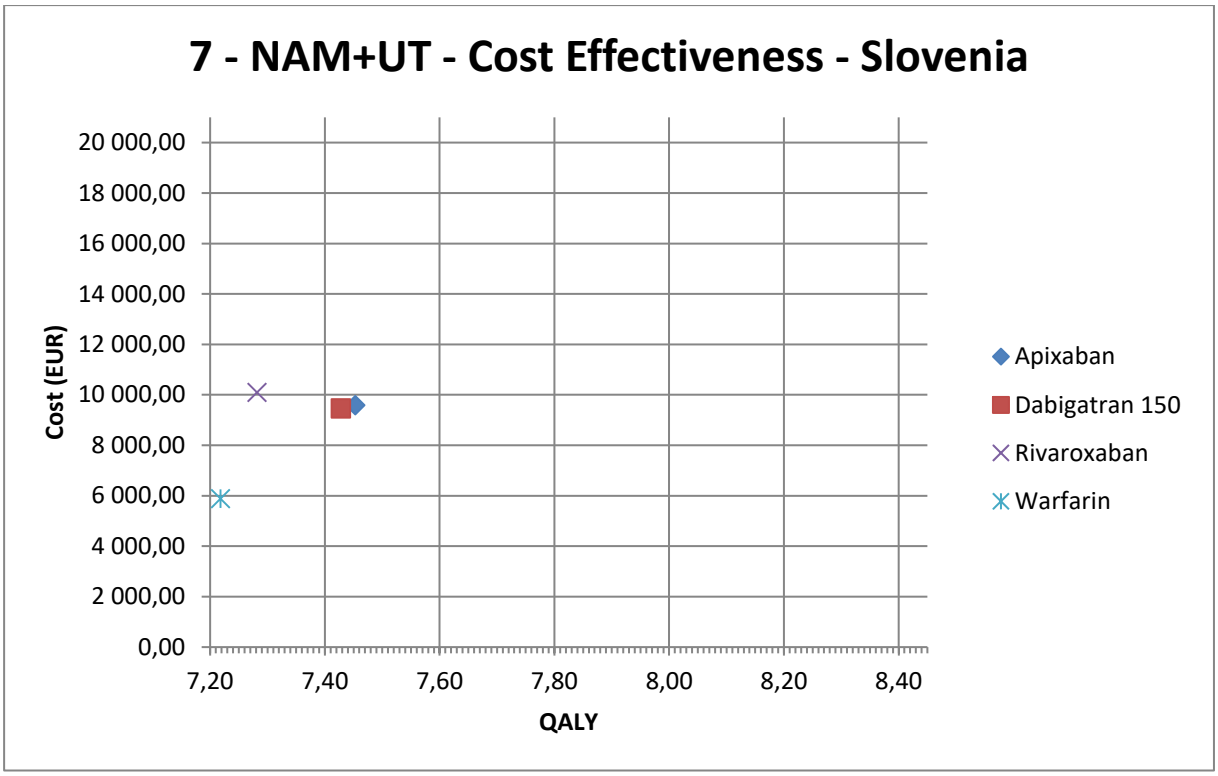


Figure 20 – Cost-Effectiveness Graph for the 3 NOAC strategies and Warfarin in Slovenia.

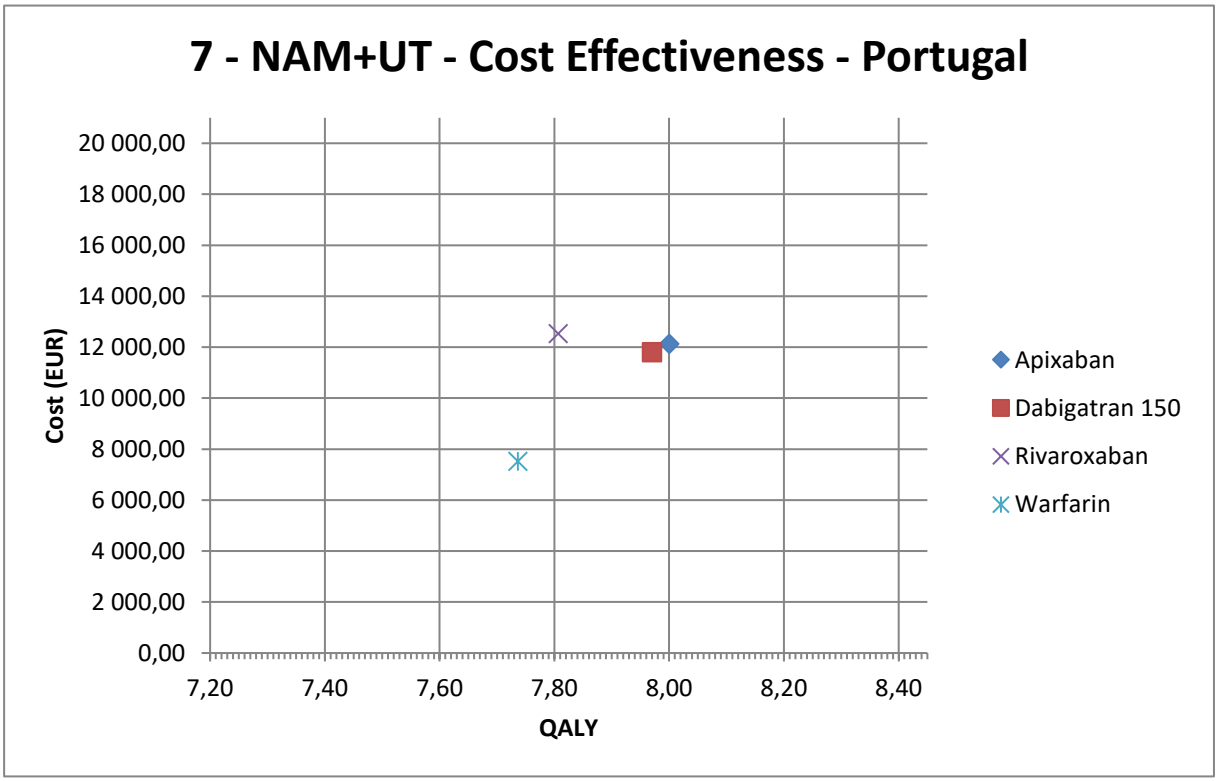


Figure 21 - Cost-Effectiveness Graph for the 3 NOAC strategies and Warfarin in Portugal.

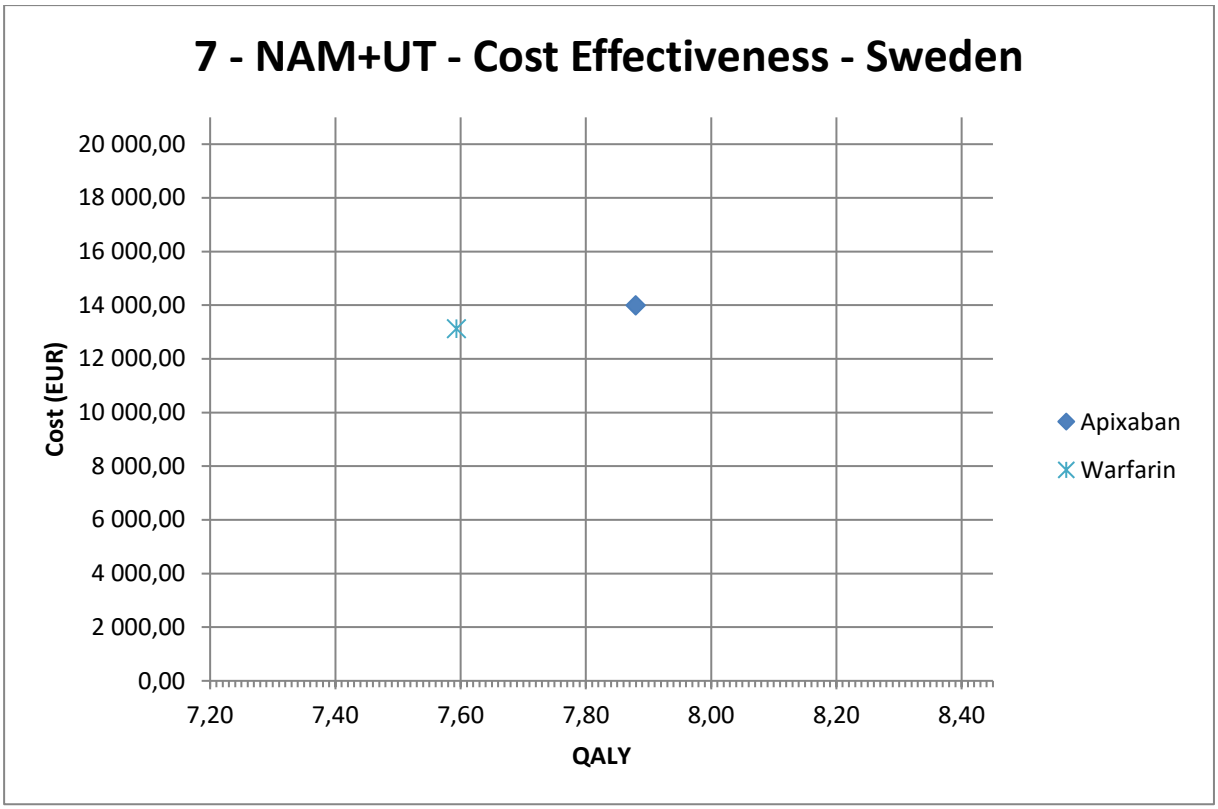


Figure 22 - Cost-Effectiveness Graph for Apixaban and Warfarin in Sweden.

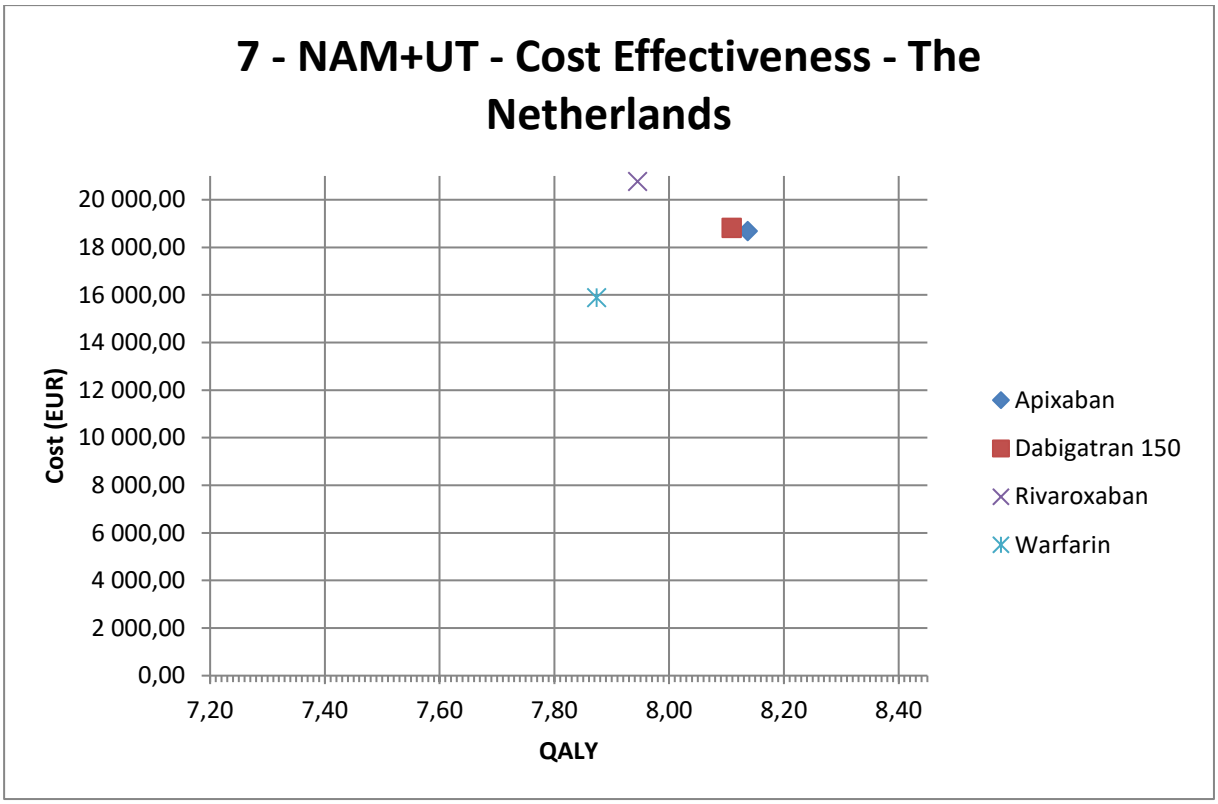


Figure 23 - Cost-Effectiveness Graph for the 3 NOAC strategies and Warfarin in The Netherlands.

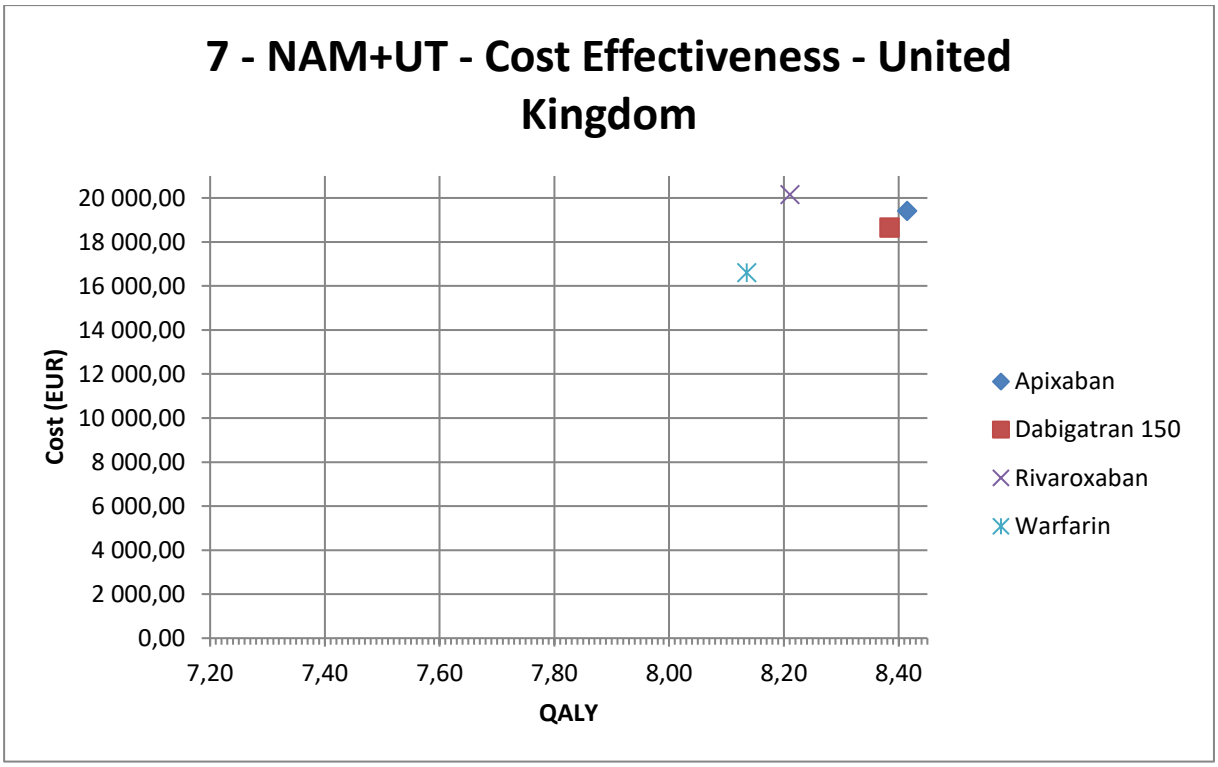


Figure 24 – Cost-Effectiveness Graph for the 3 NOAC strategies and Warfarin in The United Kingdom.

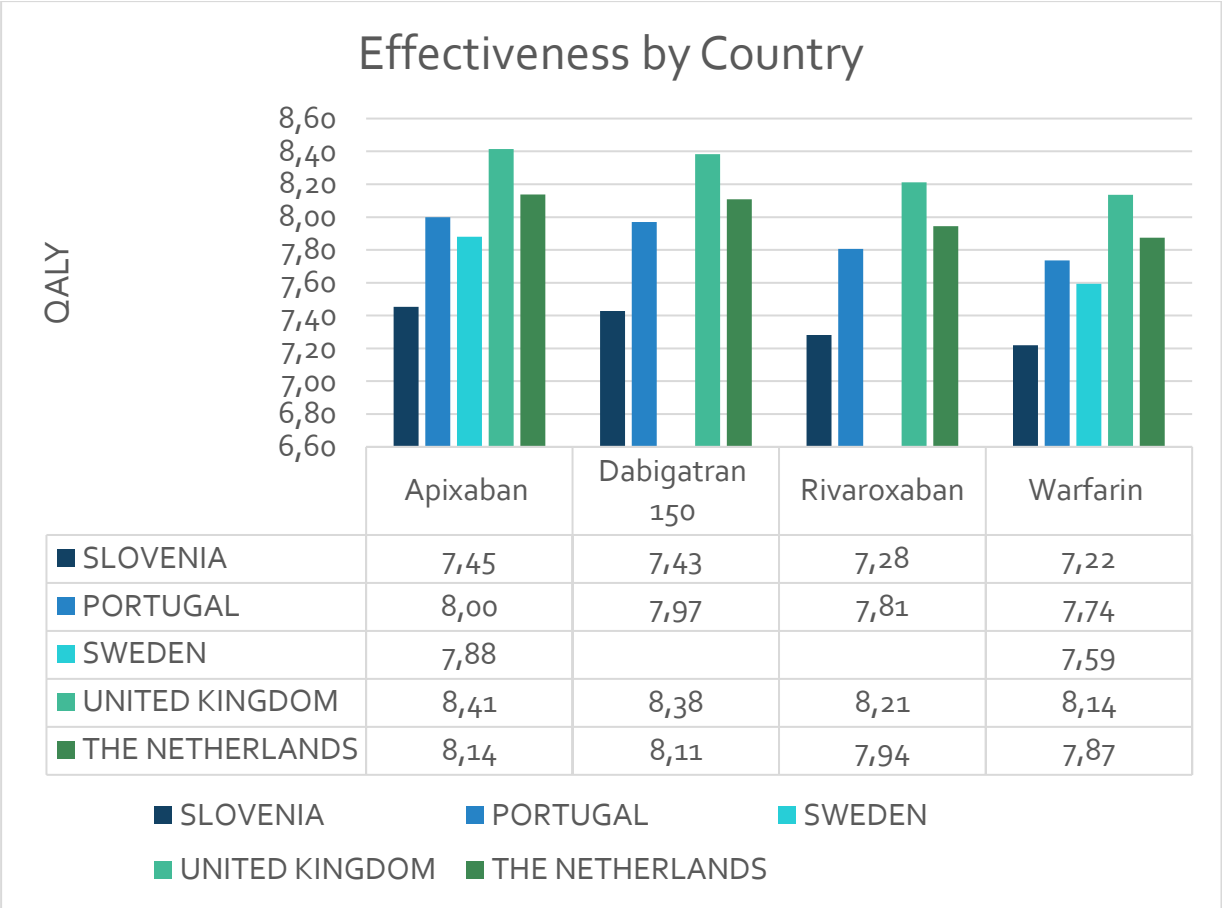


Figure 25 – National Adopted Model + Utilities, Total Effectiveness by Country.

Figure 25 shows the effectiveness of each NOAC and Warfarin in all the countries. Apixaban has the highest effectiveness in all 5 countries compared to the options. In every country where it was studied Rivaroxaban proved to be the less effective NOAC. Slovenia is the country where the drug presents less effectiveness with Apixaban showing less effectiveness in terms of QALY (7.45 QALY) than Warfarin in any of the other 4 countries (7.74;7.59;8.14;7.87). The UK has the best effectiveness results in this study and Warfarin there has the same effectiveness as the second-best effectiveness shown for Apixaban except for the UK itself, matching the Netherlands (8.14 QALY).

Even though the effectiveness results are important they don't determine what's the most cost-effective strategy in this case. To know that it is necessary to calculate the ICER or Incremental Cost-Effectiveness Ratio. It is defined by NICE as: "The difference in the change in mean costs in the population of interest divided by the difference in the change in mean outcomes in the population of interest."(40) This means that in this case is the division between the difference

in Cost from the Warfarin to NOAC and the difference between the effectiveness of the same two:

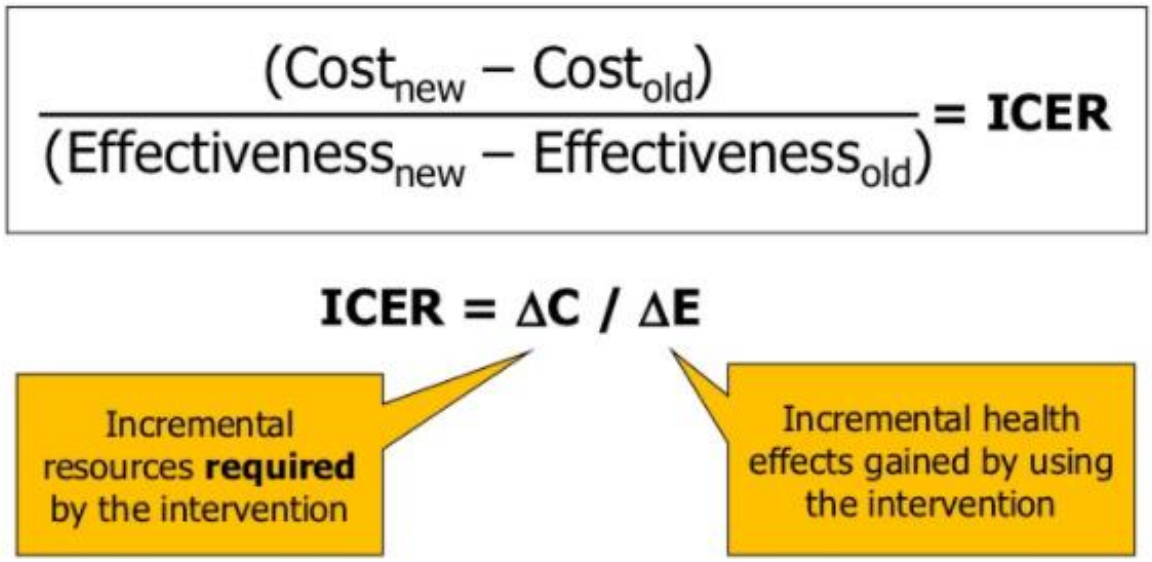


Figure 26 – Incremental Cost-Effectiveness Ratio (ICER) – Equations (adapted from: Economic Evaluation in Healthcare, Craig Mitton, François Dionne, Priority Setting and Resource Allocation)(50)**.**

ICER is then, in a Cost-utility analysis like this, synonymous with the cost per quality-adjusted life year (QALY) gained. So, with it, it is possible to know which is the best treatment strategy (with NOACs) in each country in the cases of Slovenia, Portugal, The Netherlands and the UK.

The ICER for each country and treatment strategy is shown in the next figure:

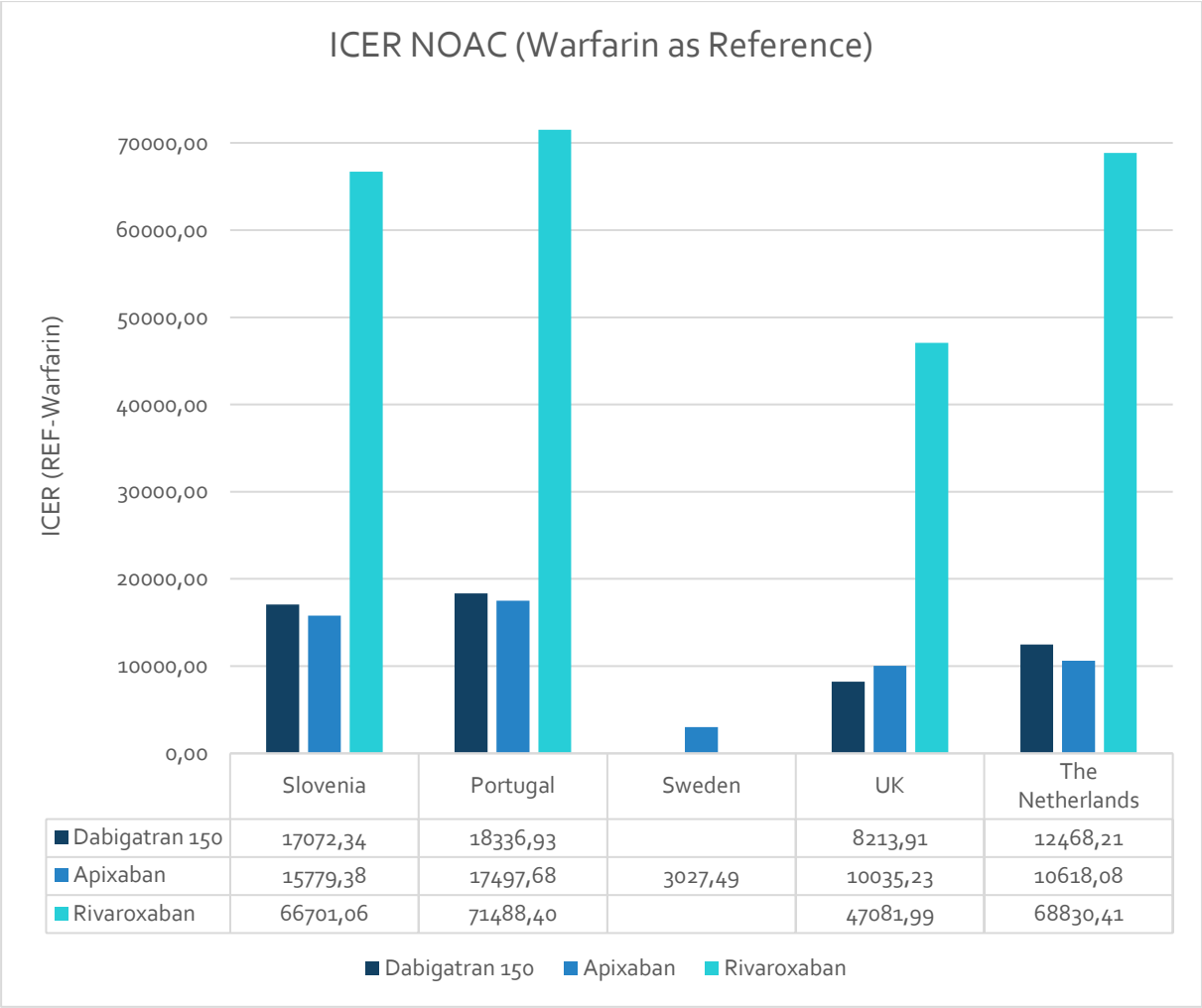


Figure 27 – Incremental Cost-Effectiveness Ratio for each treatment option in all 5 countries.

The graph shows that Apixaban has the lowest ICER of the 3 NOACs tested in 3 out of 4 countries: Slovenia, Portugal and the Netherlands. In the cost of adding one QALY to patients suffering from AF is lower with Dabigatran. Rivaroxaban has the highest cost per QALY in the 4 countries where it was tested. Dabigatran treatment is just a bit costlier than Apixaban in Slovenia, Portugal and The Netherlands and a bit less in the UK. Regarding Sweden it is not possible to know which NOAC is more cost-effective, but it is possible to acknowledge that the cost of each QALY using Warfarin as reference is relatively low.

It is also interesting to check that the cost of gaining one QALY is greater in Slovenia and Portugal than in the UK or the Netherlands. If we consider only Apixaban the same can be said regarding Sweden when comparing to every other country.

3.7 Limitations of this Study

The present study has some limitations that must be mentioned and discussed.

The main and most evident limitation is based on the fact that despite the existence of several CE analysis for the countries selected, for the purpose of this study only one from one article was taken into account. This allows the possibility that the input data used from these selected articles for these selected countries may not be the most representative for each specific country. Besides data used was not validated by comparison with other articles thoroughly.

Other important one to mention resides on the fact that the input data retrieved from each articles was specific to the model used in each article and therefore data had to be adapted to be applicable to the model used in this study, so there is the possibility that specific parameters were not perfectly matched (e.g. different definitions of haemorrhagic strokes). Also, during the process some assumptions had to be made and that is another source of possible error.

Other important fact to discuss has to do with the model used. In the study the analysis were made based on this one model and therefore it is not wise to conclude that with other model with different assumptions the results would be the same.

Also, the conclusions are, of course, limited because only 5 countries were selected for the analysis, and the study would have more robust conclusions with more countries included.

Last, but not least, only deterministic analysis were performed (so conclusions are based on deterministic results) and they were not complemented by sensitivity analysis (one-way sensitivity analysis with probabilistic sensitivity analysis) that would take into account uncertainty in the input values and predict the variations in the outcomes and therefore in the ICER. This could have implications in the final CE result and it is very important because some of the public data used as input data in this model (set as public by each country) does not correspond to the real values adding uncertainty and error to the results.

4 Conclusions

The study evaluates the influence of national-specific data in CE analysis, more specifically in cost-utility analysis for 3 NOACs and Warfarin in 5 different European settings: Portugal, Slovenia, Sweden, UK and the Netherlands.

Six types of analysis were performed using an adaptation of a Markov decision model based on one from the article: "Cost Effectiveness of Novel Oral Anticoagulants for Stroke Prevention in Atrial Fibrillation Depending on the Quality of Warfarin Anticoagulation Control" by Andrej Janžič and Mitja Kos (2014). In these 6 types of analysis a significant number of variations were made to understand the impact of different variables in the overall result. These variables were the Drug Costs, All Costs (including other clinical costs), Utilities, Mortality Tables, National Adopted Models (every variable but mortality tables) and the final simulation with all the National Specific data including the Mortality Tables. After these simulations, with the results from the later one the most CE NOAC was accessed through ICER calculation for the European settings mentioned above except Sweden because no data was available for two of the 3 studied NOACs.

More important than which NOAC was the most cost-effective for each country was to valuate as the relative impact of the different variables changed through the simulations and understand how they impact the final CE result.

An analysis of the input parameters used allowed to understand from the beginning some of the differences between the 5 settings analysed. This comparison showed that the baseline characteristics were not very different from country to country and that the drug cost was also comparable between all of them. Even though in the event cost some big differences were found. These were mainly found in the costs relative to fatal and non-fatal events. In countries such as Sweden for example fatal and non-fatal events have the same average cost while in other such as Portugal for instance a great gap between fatal and non-fatal events was observed. This is actually one of the main limitations of this study as some countries don't define different cost for fatal and for non-fatal events and instead only average data is available.

Nonetheless the analysis were made and the simple descriptive analysis of the input data shows in a certain way the variations that are seen in the results of the different simulations made which is expectable.

The simulations results demonstrated the event costs have a great impact in the simulated outcome cost for each country being the main influencer since event costs are the most different variable

between countries. They even present a bigger impact than drug cost because the later are very similar in the 5 settings studied. Nonetheless a bigger change in these would probably exponentially alter these simulated outcome costs but in the real world they are comparable, so we can conclude that between drug costs and events costs, the event costs have a bigger relative impact on the outcome costs.

The simulated outcome cost also proved to be very influenced by the mortality tables. The death probability in the ages directly related to the model used proved to be an important factor and not the mortality table as an all. These tables have from the beginning differences between the countries due to several quality-of-life and development factors that are certainly important for the overall cost-effectiveness results obtained. Nonetheless, the relative impact of the mortality input data is smaller than the one caused by the event costs.

When it comes to the simulated effectiveness outcome in real European settings the mortality tables showed a bigger relative impact on the result than the utilities itself mostly due to the small variations between countries studied in the utilities. Once again, the death probabilities between the ages of 70 years-old and 85 years-old, the ages at which the patients enter the model due to the bigger probability of event occurrence proved to have a big impact in the QALYs observed in the effectiveness outcome for each country. In this parameter for instance Sweden shows a bigger increase in effectiveness (in QALY) because it has the lowest death probability in the age interval mentioned. This was one of the reasons Sweden was still used in the study even though data for Dabigatran and Rivaroxaban was not reported.

Focusing the analysis in the drugs themselves, Rivaroxaban has the higher simulated outcome cost of the NOACs studied in every country by far. Moreover, its effectiveness is slightly closer to that of the Warfarin than to the one of the other NOACs studied. As rivaroxaban has a higher price than other NOACs in most of the countries this proves the fact that the potential of drug cost to influence the simulated outcome cost is huge as a small change in drug price changes invariably the outcome cost result. In the case of Rivaroxaban this together with the smaller effectiveness data reported results in the end in much lower cost per QALY. It is also interesting to note that the simulated outcome cost of Warfarin is higher in Sweden, The Netherlands and the United Kingdom than the simulated outcome cost for the NOACs Apixaban and Dabigatran in Portugal and Slovenia. Even tough not enough data was analysed, and further analysis is needed two groups of countries can be defined with the analysis made. Slovenia and Portugal in one and The Netherland, Sweden and the United Kingdom in the other. This happens probably due to economic and social development as well as the healthcare system particularities in these countries.

Both Apixaban and Dabigatran show closer outcome effectiveness and outcome costs to each other in every country they were both analysed. This has to do with the fact that they both have almost similar costs and effectiveness when compared to Rivaroxaban.

To fully define which NOAC was more cost effective (except in Sweden where Dabigatran and Rivaroxaban data was not reported) ICER was calculated. The ICER calculation results showed that Apixaban is the most cost-effective NOAC in Portugal, Slovenia and The Netherlands while Dabigatran is the most cost-effective in the United Kingdom. On the other hand, Rivaroxaban showed a very high cost per QALY, clearly above the threshold of € 20000 / QALY usually used by decision-makers to decide whether to reimburse a drug.

Analysing the cost per QALY among the different countries for the same medicine in a more transversal way, it is important to mention that Sweden demonstrated the lower cost per QALY in the case of Apixaban. This is a good sign in favour of Apixaban CE in this country even tough it is not possible to compare it with the other two NOACs.

Excluding Rivaroxaban, the Cost per QALY also reflects the already mentioned tendency that is it possible to distinguish between two groups of countries in this study. This is significantly lower in countries theoretically perceived as more developed such as Sweden, The Netherlands and the United Kingdom over Portugal and Slovenia.

Despite the results it is also important to take into account the main limitations of the study. These were explored and discussed. Issues such as interval of time considered in the life tables used, some adjusted input values for certain variables, the truthfulness behind some of the public reported data and more important the fact that even tough the data used was recent a study like this most of the times when published lacks update already due to changes in cost for instance were important limitations that limit the validity of the overall results.

For the future it is important that more CE studies are made to better allocate resources when it comes to healthcare. Authorities have an important role not only in making these studies to support decision makers but also in minimizing the limitations of these studies by reporting real and updated data needed to perform them. A much broader study on the factors leading to changes in CE would be very interesting to allow countries to act on the base reasons that result in the differences seen and reported in this and other publications. It is clear that this kind of studies would allow countries to optimize their systems and procedures contributing not only each country’s healthcare sustainability which is a big concern nowadays but also to better allocate resources and be able to support innovation and orphan drugs and treatments.

References

1. Grad FP. The Preamble of the Constitution of the World Health Organization. Bull World Health Organ [Internet]. 2002 [cited 2017 Oct 19];80(12):981–4. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12571728
2. Backhouse RE, Medema SG. Retrospectives: On the Definition of Economics. J Econ Perspect [Internet]. 2009 Jan [cited 2017 Oct 19];23(1):221–33. Available from: http://pubs.aeaweb.org/doi/10.1257/jep.23.1.221
3. Smith A. An Inquiry into the Nature and Causes of the Wealth of Nations [Internet]. 1904th ed. Cannan E, editor. IV. London: Methuen & Co., Ltd.; 1776 [cited 2017 Oct 19]. Available from: ttp://www.econlib.org/library/Smith/smWN12.html
4. Groenewegen P. 'political economy'. In: The New Palgrave Dictionary of Economics [Internet]. Basingstoke: Nature Publishing Group; [cited 2017 Oct 19]. p. 476–80. Available from: http://www.dictionaryofeconomics.com/article?id=pde2008_P000114
5. Carlyle T. Occasional Discourse on the N[egro] Question. Fraser's Mag republished Work Thomas Carlyle, 1904. 1849;29:348–83.
6. Mill S. On the Definition of Political Economy; and on the Method of Investigation Proper to It. In: Essays on Some Unsettled Questions of Political Economy [Internet]. 2nd ed. London: Longmans, Green, Reader, & Dyer; 1844. Available from: http://www.econlib.org/library/Mill/mlUQP5.html#Essay V. On the Definition of Political Economy.
7. Marshall A. Principles of Economics [Internet]. London: Palgrave Macmillan UK; 2013 [cited 2017 Oct 19]. Available from: http://link.springer.com/10.1057/9781137375261
8. Robbins L. An Essay on the Nature and Significance of Economic Science [Internet]. 2nd ed. London: Macmillan and Co., Ltd; 1932. 15 p. Available from: https://pt.scribd.com/document/14242989/An-Essay-on-the-Nature-and-Significance-of-Economic-Science-Lionel-Robbins
9. Backhouse RE, Medema SG. Defining Economics: The Long Road to Acceptance of the Robbins Definition [Internet]. Vol. 76, Economica. WileyThe London School of Economics and Political ScienceThe Suntory and Toyota International Centres for Economics and Related Disciplines; [cited 2017 Oct 19]. p. 805–20. Available from: https://www.jstor.org/stable/40268907
10. Robbins L. An Essay on the Nature and Significance of Economic Science [Internet]. 2nd ed. London: Macmillan and Co., Ltd; 1932. 16 p. Available from: https://pt.scribd.com/document/14242989/An-Essay-on-the-Nature-and-Significance-of-Economic-Science-Lionel-Robbins
11. Begg DKH, Fischer S, Dornbusch R. Economics. McGraw Hill Education; 2005. 674 p.
12. Morris S (Stephen), Morris S (Stephen). Economic analysis in health care. John Wiley & Sons; 2012.
13. Parkin D. Principles of health economics including: the notions of scarcity, supply and demand, distinctions between need and demand, opportunity cost, discounting, time horizons, margins, efficiency and equity. In: Public Health Textbook [Internet].

Available from: https://www.healthknowledge.org.uk/public-health-textbook/medical-sociology-policy-economics/4d-health-economics/principles-he

14. Opportunity Cost [Internet]. Investopedia. [cited 2017 Oct 19]. Available from: http://www.investopedia.com/terms/o/opportunitycost.asp

15. Buchanan JM. opportunity cost. In: The New Palgrave Dictionary of Economics [Internet]. Basingstoke: Nature Publishing Group; [cited 2017 Oct 19]. p. 198–201. Available from: http://www.dictionaryofeconomics.com/article?id=pde2008_O000029

16. Definition of opportunity cost [Internet]. Oxford Dictionaries. [cited 2017 Oct 19]. Available from: https://en.oxforddictionaries.com/definition/us/opportunity_cost

17. MUSHKIN SJ. Toward a definition of health economics. Public Heal reports (Washington, DC 1896) [Internet]. 1958 Sep [cited 2017 Oct 19];73(9):785–93. Available from: http://www.ncbi.nlm.nih.gov/pubmed/13579116

18. Klarman HE. The Distinctive Economic Characteristics of Health Services. J Health Hum Behav [Internet]. 1963 [cited 2017 Oct 19];4(1):44. Available from: http://www.jstor.org/stable/2948972?origin=crossref

19. Culyer AJ. The Nature of the Commodity 'Health Care' and its Efficient Allocation [Internet]. Vol. 23, Oxford Economic Papers. Oxford University Press; [cited 2017 Oct 19]. p. 189–211. Available from: http://www.jstor.org/stable/2662234

20. Pauly M V. Medical staff characteristics and hospital costs. J Hum Resour [Internet]. 1978 [cited 2017 Oct 19];13 Suppl:77–111. Available from: http://www.ncbi.nlm.nih.gov/pubmed/722072

21. Pauly M V. Is medical care different? Old questions, new answers. J Health Polit Policy Law [Internet]. 1988 [cited 2017 Oct 19];13(2):227–37. Available from: http://www.ncbi.nlm.nih.gov/pubmed/3385166

22. Folland S, Goodman AC, Stano M. The economics of health and health care. New York : Macmillan Pub. Co.; 1993. 726 p.

23. Culyer AJ (Anthony J., Newhouse JP, Pauly M V., McGuire TG, Barros PP. Handbook of health economics. Elsevier; 2000.

24. Grossman M. On the Concept of Health Capital and the Demand for Health [Internet]. Vol. 80, Journal of Political Economy. The University of Chicago Press; [cited 2017 Oct 19]. p. 223–55. Available from: http://www.jstor.org/stable/1830580

25. Bloom G, Standing H, Lloyd R. Markets, information asymmetry and health care: Towards new social contracts. Soc Sci Med [Internet]. 2008 May 1 [cited 2017 Oct 19];66(10):2076–87. Available from: http://www.sciencedirect.com/science/article/pii/S0277953608000592

26. Arrow KJ. Uncertainty and the welfare economics of medical care. 1963. Bull World Health Organ [Internet]. 2004 Feb [cited 2017 Oct 19];82(2):141–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15042238

27. Carroll S, Carroll R. Why health economics is becoming ever more important in the industry. Pharm J [Internet]. 2009 [cited 2017 Oct 19]; Available from: http://www.pharmaceutical-journal.com/opinion/comment/why-health-economics-is-becoming-ever-more-important-in-the-industry/10342006.article

28. Ferraz MB. The importance of health economics in a world of proportionally increasing scarce resources. São Paulo Med J [Internet]. 1995 [cited 2017 Oct 19];113:54. Available

from: http://www.scielo.br/pdf/spmj/v113n2s0/v113n2a31.pdf

29. Hale J. What contribution can health economics make to health promotion? Health Promot Int [Internet]. 2000 Dec 1 [cited 2017 Oct 19];15(4):341–8. Available from: https://academic.oup.com/heapro/article-lookup/doi/10.1093/heapro/15.4.341

30. Morrison A, Wertheimer AI. Pharmacoeconomics: A Primer for the Pharmaceutical Industry. 1st ed. Philadelphia: Temple University; 2002. 1-72 p.

31. TRASK LS. Chapter 1. Pharmacoeconomics: Principles, Methods, and Applications. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, editors. Pharmacotherapy: A Pathophysiologic Approach, 8e [Internet]. New York, NY: The McGraw-Hill Companies; 2011. Available from: accesspharmacy.mhmedical.com/content.aspx?aid=7965001

32. Ryder HF, McDonough C, Tosteson ANA, Lurie JD. Decision Analysis and Cost-effectiveness Analysis. Semin Spine Surg [Internet]. 2009 Dec [cited 2017 Oct 19];21(4):216–22. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23966758

33. Decision Tree [Internet]. Investopedia. [cited 2017 Oct 19]. Available from: http://www.investopedia.com/terms/d/decision-tree.asp

34. Glossary of Frequently Encountered Terms in Health Economics [Internet]. Health Economics Information Resources: A Self-Study Course - . U.S. National Library of Medicine; [cited 2017 Oct 19]. Available from: https://www.nlm.nih.gov/nichsr/edu/healthecon/glossary.html#Cost

35. Plumridge RJ, Wojnar-Horton RE. A review of the pharmacoeconomics of pharmaceutical care. Pharmacoeconomics [Internet]. 1998 Aug [cited 2017 Oct 23];14(2):175–89. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10186458

36. Arias M, Díez FJ. Cost-effectiveness Analysis with Influence Diagrams. Methods Inf Med [Internet]. 2015 Mar 12 [cited 2017 Oct 23];54(4):353–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25762363

37. Deeley K. Exploring Risk Contagion Using Graph Theory and Markov Chains. MathWorks [Internet]. 2007 [cited 2017 Oct 23]; Available from: https://www.mathworks.com/company/newsletters/articles/exploring-risk-contagion-using-graph-theory-and-markov-chains.html

38. Whitehead SJ, Ali S. Health outcomes in economic evaluation: the QALY and utilities. Br Med Bull [Internet]. 2010 Dec 1 [cited 2017 Oct 23];96(1):5–21. Available from: https://academic.oup.com/bmb/article-lookup/doi/10.1093/bmb/ldq033

39. Kind P, Elston Lafata J, Matuszewski K, Raisch D. The Use of QALYs in Clinical and Patient Decision-Making: Issues and Prospects. Value Heal [Internet]. 2009 [cited 2017 Nov 5];12:S27–30. Available from: http://www.valueinhealthjournal.com/article/S1098-3015(10)60050-2/pdf?_returnURL=http%3A%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS1098301510600502%3Fshowall%3Dtrue

40. Glossary | NICE. [cited 2017 Oct 23]; Available from: https://www.nice.org.uk/Glossary

41. Weinstein MC, Torrance G, McGuire A. QALYs: The Basics. Value Heal [Internet]. 2009 Mar [cited 2017 Oct 23];12:S5–9. Available from: http://linkinghub.elsevier.com/retrieve/pii/S1098301510600460

42. WHO | Metrics: Disability-Adjusted Life Year (DALY). WHO [Internet]. 2014 [cited

2017 Oct 23]; Available from: http://www.who.int/healthinfo/global_burden_disease/metrics_daly/en/

43. Airoldi M. Gains in QALYs vs DALYs averted: the troubling implications of using residual life expectancy. [cited 2017 Oct 23]; Available from: www.lse.ac.uk/collections/LSEHealth/

44. Janzic A, Kos M. Cost Effectiveness of Novel Oral Anticoagulants for Stroke Prevention in Atrial Fibrillation Depending on the Quality of Warfarin Anticoagulation Control. Pharmacoeconomics [Internet]. 2015 Apr 16 [cited 2017 Oct 23];33(4):395–408. Available from: http://link.springer.com/10.1007/s40273-014-0246-7

45. Blann A. Non-Vitamin K Oral Anticoagulants (NOACs) A Review of Clinical Management and Laboratory Issues. Curr Vasc Pharmacol [Internet]. 2016 [cited 2017 Oct 23];14(3):220–36. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26059459

46. Britt RP, James AH, Raskino CL, Thompson SG. Factors affecting the precision of warfarin treatment. J Clin Pathol [Internet]. 1992 Nov [cited 2017 Oct 23];45(11):1003–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/1452773

47. Costa J, Fiorentino F, Caldeira D, Inês M, Lopes Pereira C, Pinheiro L, et al. Custo-efetividade dos novos anticoagulantes orais na fibrilhação auricular em Portugal. Rev Port Cardiol [Internet]. 2015 Dec [cited 2017 Oct 23];34(12):723–37. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26616542

48. Lanitis T, Kongnakorn T, Jacobson L, De Geer A. Cost-effectiveness of Apixaban versus Warfarin and Aspirin in Sweden for Stroke Prevention in Patients with Atrial Fibrillation. Thromb Res [Internet]. 2014 Aug [cited 2017 Oct 23];134(2):278–87. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24935675

49. Verhoef TI, Redekop WK, Hasrat F, de Boer A, Maitland-van der Zee AH. Cost Effectiveness of New Oral Anticoagulants for Stroke Prevention in Patients with Atrial Fibrillation in Two Different European Healthcare Settings. Am J Cardiovasc Drugs [Internet]. 2014 Dec 18 [cited 2017 Oct 23];14(6):451–62. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25326294

50. Mitton C, Dionne F. Economic Evaluation in Healthcare. Centre for Healthcare Management, University of British Columbia; 2011.

Attachments

A1.1 Portugal's Baseline Parameters

Portugal's Input Parameter	Point estimate
Baseline rate of ischaemic stroke (%/y)	1,23
Disabling ischaemic strokes (%)	40,2
Fatal ischaemic strokes (%)	8,2
Baseline rate of intracranial haemorrhage (%/y)	0,79
Disabling intracranial haemorrhages (%)	31,8
Fatal intracranial haemorrhages (%)	51,6
Discontinuation at nondisabling intracranial haemorrhage (%)	14,3
Baseline rate of systemic embolism (%/y)	0,14
Baseline rate of major haemorrhage (%/y)	2,59
Fatal major haemorrhage (%)	5,1
Discontinuation at nonfatal major haemorrhage (%)	14,3
Baseline rate of myocardial infarction (%/y)	0,74
Fatal myocardial infarctions (%)	9,9
Relative risk for death of disabled vs nondisabled persons	2,21
Parameter in CHADS2 model	
Thromboembolic events	0,375
Haemorrhagic events	0,253
Parameter of TTR model	
Thromboembolic events	-0,016
Haemorrhagic events	-0,016
Relative risks for clinical events without anticoagulation treatment	
Thromboembolic events	3,03
Haemorrhagic events	0,43
Difference in TTR between genotype-guided and standard dosing of warfarin in the first month	10,2

A1.2 Portugal's Costs and Utilities Input Parameters

Portugal's Input Parameters	Point estimate
Costs (EUR)	
Annual drug costs	
Warfarin	29,22
Dabigatran	898,52
Rivaroxaban	901,55
Apixaban	880,25
Monitoring costs	
Warfarin, maintenance phase, per year	342,24
NOAC, per year	111,16
Event costs	
Ischaemic stroke	
Non-fatal	8653,26
Fatal	870
Intracranial haemorrhage	
Non-fatal	13779,62
Fatal	10419,64
Systemic embolism	3937,93
Extracranial major haemorrhage	2121
Myocardial infarction	4158*
Annual cost for disabled patients	534,84
Utilities	
Baseline utility of nondisabled patients with atrial fibrillation	0,772
Disabled patients after neurological event	0,399
Events disutility for one month	
Ischaemic stroke and intracranial haemorrhage	-0,2074
Extracranial major haemorrhage	-0,07555
Other events (systemic embolism or myocardial infarction)	-0,1455

A1.3 Portugal's Mortality Tables

Age	Probability
0	0,002961
1	2,20E-04
2	1,51E-04
3	1,49E-04
4	8,70E-05
5	1,28E-04
6	9,10E-05
7	8,50E-05
8	7,80E-05
9	7,70E-05
10	7,60E-05
11	1,12E-04
12	8,40E-05
13	7,60E-05
14	1,21E-04
15	1,69E-04
16	2,12E-04
17	1,86E-04
18	3,03E-04
19	3,15E-04
20	3,15E-04
21	3,76E-04
22	3,25E-04
23	3,45E-04
24	3,30E-04
25	3,84E-04
26	3,99E-04
27	4,36E-04
28	4,57E-04
29	5,42E-04
30	4,87E-04
31	4,62E-04
32	5,40E-04
33	5,62E-04
34	6,21E-04
35	7,73E-04
36	7,32E-04
37	0,0008
38	0,000966
39	0,001055
40	0,00104
41	0,001433
42	0,001513
43	0,001685
44	0,001824
45	0,002001
46	0,002387
47	0,002538
48	0,002565
49	0,002932
50	0,003259
51	0,003452
52	0,004112
53	0,004152
54	0,004391
55	0,004894
56	0,005272
57	0,005435
58	0,005919
59	0,006052
60	0,006747
61	0,007384
62	0,007645
63	0,007928
64	0,008835
65	0,009592
66	0,010313
67	0,010999
68	0,012913
69	0,013917
70	0,015419
71	0,016455
72	0,017784
73	0,019552
74	0,022641
75	0,025876
76	0,028275
77	0,031882
78	0,035443
79	0,039784
80	0,045929
81	0,052058
82	0,059614
83	0,071349
84	0,086843
85	0,106514
86	0,125364
87	0,146137
88	0,168139
89	0,192019
90	0,22019
91	0,247927
92	0,277808
93	0,309787
94	0,343778
95	0,379657
96	0,417254
97	0,456359
98	0,496718
99	0,538035
100	0,579973

A2.1 Slovenia's Baseline Parameters

Slovenian's Input Parameters	Point estimate
Baseline rate of ischaemic stroke (%/y)	1,23
Disabling ischaemic strokes (%)	40,2
Fatal ischaemic strokes (%)	8,2
Baseline rate of intracranial haemorrhage (%/y)	0,79
Disabling intracranial haemorrhages (%)	31,8
Fatal intracranial haemorrhages (%)	51,6
Discontinuation at nondisabling intracranial haemorrhage (%)	14,3
Baseline rate of systemic embolism (%/y)	0,14
Baseline rate of major haemorrhage (%/y)	2,59
Fatal major haemorrhage (%)	5,1
Discontinuation at nonfatal major haemorrhage (%)	14,3
Baseline rate of myocardial infarction (%/y)	0,74
Fatal myocardial infarctions (%)	9,9
Relative risk for death of disabled vs nondisabled persons	2,21
Parameter in CHADS2 model	
Thromboembolic events	0,375
Haemorrhagic events	0,253
Parameter of TTR model	
Thromboembolic events	-0,016
Haemorrhagic events	-0,016
Relative risks for clinical events without anticoagulation treatment	
Thromboembolic events	3,03
Haemorrhagic events	0,43
Difference in TTR between genotype-guided and standard dosing of warfarin in the first month	10,2

A2.2 Slovenia's Costs and Utilities Input Parameters

Slovenia's Input Parameters	Point estimate
Costs (EUR)	
Annual drug costs	
Warfarin	23,00
Dabigatran	744,62
Rivaroxaban	745,11
Apixaban	724,05
Monitoring costs	
Warfarin, initial phase (standard dosing)	85,00
Warfarin, initial phase (genotype-guided dosing)	63,75
Warfarin, maintenance phase	147,99
NOAC, first year	25,5
NOAC, following years	8,5
Cost of pharmacogenetic test	50
Event costs	
Ischaemic stroke	
Nondisabling	3878
Disabling	7277
Fatal	870
Intracranial haemorrhage	
Nondisabling	5670
Disabling	9069
Fatal	870
Systemic embolism	3206
Extracranial major haemorrhage	2121
Myocardial infarction	4158
Annual cost for disabled patients	3399
Utilities	
Baseline utility of nondisabled patients with atrial fibrillation	0,774
Disabled patients after neurological event	0,401

	Events disutility for one month		
		Ischaemic stroke and intracranial haemorrhage	-0,1385
		Extracranial major haemorrhage	-0,0624
		Other events (systemic embolism or myocardial infarction)	-0,1247

A2.3 Slovenia's Mortality Tables

Age	Probability
0	0,002819
1	2,95E-04
2	2,67E-04
3	2,25E-04
4	1,82E-04
5	1,50E-04
6	1,30E-04
7	1,12E-04
8	9,70E-05
9	9,00E-05
10	9,40E-05
11	1,12E-04
12	1,42E-04
13	1,79E-04
14	2,24E-04
15	2,82E-04
16	3,47E-04
17	4,24E-04
18	5,23E-04
19	6,33E-04
20	7,26E-04
21	7,79E-04
22	7,87E-04
23	7,48E-04
24	6,97E-04
25	6,71E-04
26	6,81E-04
27	7,07E-04
28	7,38E-04
29	7,55E-04
30	7,58E-04
31	7,60E-04
32	7,72E-04
33	7,96E-04
34	8,26E-04
35	8,64E-04
36	9,14E-04
37	0,001001
38	0,001123
39	0,001262
40	0,001407
41	0,001551
42	0,001697
43	0,001884
44	0,002119
45	0,002385
46	0,002699
47	0,003065
48	0,003434
49	0,003795
50	0,00415
51	0,004513
52	0,004945
53	0,005449
54	0,005985
55	0,006505
56	0,006973
57	0,007445
58	0,00799
59	0,008627
60	0,009353
61	0,010154
62	0,011064
63	0,012071
64	0,013031
65	0,014001
66	0,015177
67	0,016608
68	0,018265
69	0,02018
70	0,022308
71	0,024725
72	0,027518
73	0,030665
74	0,034053
75	0,037803
76	0,04187
77	0,046255
78	0,05123
79	0,056767
80	0,062773
81	0,069625
82	0,077889
83	0,087384
84	0,097279
85	0,107359
86	0,118066
87	0,130653
88	0,14528
89	0,162559
90	0,181862
91	0,2017
92	0,222628
93	0,241513
94	0,258745
95	0,278357
96	0,300948
97	0,323598
98	0,346634
99	0,370063
100	0,390104

A3.1 Sweden's Baseline Parameters

Sweden's Input Parameters	Point estimate
Baseline rate of ischaemic stroke (%/y)	1,23
Disabling ischaemic strokes (%)	40,2
Fatal ischaemic strokes (%)	8,2
Baseline rate of intracranial haemorrhage (%/y)	0,79
Disabling intracranial haemorrhages (%)	31,8
Fatal intracranial haemorrhages (%)	51,6
Discontinuation at nondisabling intracranial haemorrhage (%)	14,3
Baseline rate of systemic embolism (%/y)	0,14
Baseline rate of major haemorrhage (%/y)	2,59
Fatal major haemorrhage (%)	5,1
Discontinuation at nonfatal major haemorrhage (%)	14,3
Baseline rate of myocardial infarction (%/y)	0,74
Fatal myocardial infarctions (%)	9,9
Relative risk for death of disabled vs nondisabled persons	2,21
Parameter in CHADS2 model	
Thromboembolic events	0,375
Haemorrhagic events	0,253
Parameter of TTR model	
Thromboembolic events	-0,016
Haemorrhagic events	-0,016
Relative risks for clinical events without anticoagulation treatment	
Thromboembolic events	3,03
Haemorrhagic events	0,43
Difference in TTR between genotype-guided and standard dosing of warfarin in the first month	10,2

A3.2 Sweden's Cost and Utilities Input Parameters

Sweden's Input parameter	Point estimate
Costs (EUR)	
Annual drug costs	
Warfarin	82,62
Dabigatran	No data
Rivaroxaban	No data
Apixaban	796,44
Monitoring costs	
Warfarin, maintenance phase, per year	500,9
NOAC, per year	0
Event costs	
Ischaemic stroke	
Non-fatal and fatal (acute)	10495,31
Intracranial haemorrhage	
Non-fatal and fatal (acute)	10495,31
Systemic embolism	3722,42
Extracranial major haemorrhage	4073,89
Myocardial infarction	10499,92
Annual cost for disabled patients	1738,1
Utilities	
Baseline utility of nondisabled patients with atrial fibrillation	0,745
Disabled patients after neurological event	0,595
Events disutility for one month	
Ischaemic stroke and intracranial haemorrhage	-0,15
Extracranial major haemorrhage	-0,07555
Other events (systemic embolism or myocardial infarction)	-0,02552

A3.3 Sweden's Mortality Table

Age	Probability
0	0,00241
1	0,00019
2	0,0001
3	0,00011
4	0,0001
5	0,00006
6	0,00008
7	0,00008
8	0,00008
9	0,00006
10	0,00008
11	0,00007
12	0,00007
13	0,00012
14	0,00011
15	0,00013
16	0,0002
17	0,00024
18	0,00029
19	0,00036
20	0,00038
21	0,00043
22	0,00044
23	0,00044
24	0,00051
25	0,00049
26	0,00053
27	0,00051
28	0,00049
29	0,00054
30	0,00049
31	0,00054
32	0,00052
33	0,00058
34	0,00058
35	0,00057
36	0,00059
37	0,00062
38	0,00064
39	0,00068
40	0,00074
41	0,00082
42	0,00088
43	0,00091
44	0,00108
45	0,00118
46	0,00133
47	0,00152
48	0,00158
49	0,00186
50	0,0021
51	0,00223
52	0,00239
53	0,00293
54	0,00307
55	0,00346
56	0,0037
57	0,00405
58	0,00447
59	0,00504
60	0,00553
61	0,00617
62	0,00654
63	0,00746
64	0,00814
65	0,00912
66	0,01024
67	0,01091
68	0,01215
69	0,01344
70	0,01455
71	0,01645
72	0,0176
73	0,0199
74	0,0225
75	0,02512
76	0,02819
77	0,03132
78	0,03516
79	0,03922
80	0,04557
81	0,05079
82	0,05766
83	0,06597
84	0,07465
85	0,08483
86	0,09539
87	0,10806
88	0,12104
89	0,14004
90	0,15313
91	0,17363
92	0,19274
93	0,2127
94	0,23131
95	0,25285
96	0,27617
97	0,3009
98	0,32703
99	0,35451
100	0,38331

A4.1 The Netherlands' Baseline Parameters

The Netherlands' Input Parameters	Point estimate
Baseline rate of ischaemic stroke (%/y)	1,23
Disabling ischaemic strokes (%)	40,2
Fatal ischaemic strokes (%)	8,2
Baseline rate of intracranial haemorrhage (%/y)	0,79
Disabling intracranial haemorrhages (%)	31,8
Fatal intracranial haemorrhages (%)	51,6
Discontinuation at nondisabling intracranial haemorrhage (%)	14,3
Baseline rate of systemic embolism (%/y)	0,14
Baseline rate of major haemorrhage (%/y)	2,59
Fatal major haemorrhage (%)	5,1
Discontinuation at nonfatal major haemorrhage (%)	14,3
Baseline rate of myocardial infarction (%/y)	0,74
Fatal myocardial infarctions (%)	9,9
Relative risk for death of disabled vs nondisabled persons	2,21
Parameter in CHADS2 model	
Thromboembolic events	0,375
Haemorrhagic events	0,253
Parameter of TTR model	
Thromboembolic events	-0,016
Haemorrhagic events	-0,016
Relative risks for clinical events without anticoagulation treatment	
Thromboembolic events	3,03
Haemorrhagic events	0,43
Difference in TTR between genotype-guided and standard dosing of warfarin in the first month	10,2

A4.2 The Netherlands' Cost and Utilities Input Parameters

The Netherlands' Input Parameters	Point estimate
Costs (EUR)	
Annual drug costs	
Warfarin	18
Dabigatran	816
Rivaroxaban	768
Apixaban	816
Monitoring costs	
Warfarin, maintenance phase, per year	176,46
NOAC, per year	41,52
Event costs	
Ischaemic stroke	
Non-fatal and fatal*	14750
Intracranial haemorrhage	
Non-fatal and fatal*	25,047
Systemic embolism	990
Extracranial major haemorrhage	13690
Myocardial infarction	5021
Annual cost for disabled patients	5760
Utilities	
Baseline utility of nondisabled patients with atrial fibrillation	0,81
Disabled patients after neurological event	0,436
Events disutility for one month	
Ischaemic stroke and intracranial haemorrhage	-0,1385
Extracranial major haemorrhage	-0,06
Other events (systemic embolism or myocardial infarction)	-0,1247

A4.3 The Netherlands' Mortality Table

Age	Probability
0	0,004189
1	0,000307
2	0,000191
3	0,000159
4	0,000123
5	0,000107
6	9,12E-05
7	8,41E-05
8	7,91E-05
9	8,01E-05
10	8,61E-05
11	8,86E-05
12	9,78E-05
13	0,000115
14	0,000136
15	0,000162
16	0,000189
17	0,000227
18	0,000266
19	0,000313
20	0,000338
21	0,000335
22	0,000342
23	0,00034
24	0,000333
25	0,000333
26	0,000342
27	0,000358
28	0,00038
29	0,000413
30	0,000434
31	0,000462
32	0,000494
33	0,000521
34	0,000549
35	0,000594
36	0,000648
37	0,000708
38	0,00078
39	0,000857
40	0,000937
41	0,001031
42	0,001144
43	0,001262
44	0,001405
45	0,001565
46	0,001761
47	0,001987
48	0,002242
49	0,002502
50	0,002783
51	0,003067
52	0,003392
53	0,003713
54	0,004064
55	0,004418
56	0,004828
57	0,005293
58	0,005848
59	0,006387
60	0,006977
61	0,007669
62	0,008397
63	0,009178
64	0,010038
65	0,010982
66	0,012034
67	0,013245
68	0,014647
69	0,016159
70	0,017971
71	0,020064
72	0,02239
73	0,025093
74	0,028246
75	0,031754
76	0,035651
77	0,040083
78	0,045017
79	0,050582
80	0,056879
81	0,063819
82	0,071634
83	0,080411
84	0,090172
85	0,100793
86	0,112706
87	0,126209
88	0,1406
89	0,15659
90	0,174124
91	0,192615
92	0,213524
93	0,232123
94	0,251785
95	0,27744
96	0,302114
97	0,328034
98	0,355148
99	0,383391
100	0,41268

A5.1 United Kingdom's Baseline Parameters

United Kingdom's Input Parameters	Point estimate
Baseline rate of ischaemic stroke (%/y)	1,23
Disabling ischaemic strokes (%)	40,2
Fatal ischaemic strokes (%)	8,2
Baseline rate of intracranial haemorrhage (%/y)	0,79
Disabling intracranial haemorrhages (%)	31,8
Fatal intracranial haemorrhages (%)	51,6
Discontinuation at nondisabling intracranial haemorrhage (%)	14,3
Baseline rate of systemic embolism (%/y)	0,14
Baseline rate of major haemorrhage (%/y)	2,59
Fatal major haemorrhage (%)	5,1
Discontinuation at nonfatal major haemorrhage (%)	14,3
Baseline rate of myocardial infarction (%/y)	0,74
Fatal myocardial infarctions (%)	9,9
Relative risk for death of disabled vs nondisabled persons	2,21
Parameter in CHADS2 model	
Thromboembolic events	0,375
Haemorrhagic events	0,253
Parameter of TTR model	
Thromboembolic events	-0,016
Haemorrhagic events	-0,016
Relative risks for clinical events without anticoagulation treatment	
Thromboembolic events	3,03
Haemorrhagic events	0,43
Difference in TTR between genotype-guided and standard dosing of warfarin in the first month	10,2

A5.2 United Kingdom's Cost and Utilities Input Parameters

United Kingdom's Input Parameters	**Point estimate**
Costs (EUR)	
Annual drug costs	
Warfarin	53,64
Dabigatran	984
Rivaroxaban	936
Apixaban	984
Monitoring costs	
Warfarin, maintenance phase, per year	516,8
NOAC, per year	121,6
Event costs	
Ischaemic stroke	
Non-fatal and fatal	14750
Intracranial haemorrhage	
Non-fatal and fatal	14531
Systemic embolism	2182
Extracranial major haemorrhage	2256
Myocardial infarction	1852
Annual cost for disabled patients	9360
Utilities	
Baseline utility of nondisabled patients with atrial fibrillation	0,81
Disabled patients after neurological event	0,436*
Events disutility for one month	
Ischaemic stroke and intracranial haemorrhage	-0,1385
Extracranial major haemorrhage	-0,06
Other events (systemic embolism or myocardial infarction)	-0,1247

A5.3 United Kingdom's Mortality Table

Age	Probability
0	0,003862
1	0,000291
2	0,000152
3	0,000118
4	0,00009
5	7,95E-05
6	0,000082
7	8,75E-05
8	0,00007
9	0,000077
10	8,35E-05
11	0,000077
12	0,00008
13	0,000111
14	0,000116
15	0,000147
16	0,000183
17	0,000221
18	0,000302
19	0,00034
20	0,000328
21	0,000344
22	0,000336
23	0,000382
24	0,000373
25	0,000411
26	0,000442
27	0,000447
28	0,000475
29	0,000509
30	0,000551
31	0,000585
32	0,00065
33	0,000666
34	0,000739
35	0,00081
36	0,000864
37	0,000924
38	0,001056
39	0,001112
40	0,001232
41	0,00131
42	0,001422
43	0,001509
44	0,001669
45	0,001827
46	0,00192
47	0,002087
48	0,002217
49	0,002447
50	0,002692
51	0,002891
52	0,003118
53	0,003406
54	0,003736
55	0,004132
56	0,00449
57	0,004996
58	0,005424
59	0,006004
60	0,006668
61	0,007216
62	0,007931
63	0,00868
64	0,009404
65	0,010196
66	0,010805
67	0,011995
68	0,013311
69	0,014798
70	0,016356
71	0,018084
72	0,020656
73	0,022923
74	0,025637
75	0,028105
76	0,031221
77	0,034436
78	0,038548
79	0,043316
80	0,049668
81	0,055537
82	0,063528
83	0,07162
84	0,081139
85	0,092306
86	0,10347
87	0,116852
88	0,131528
89	0,147775
90	0,166254
91	0,183286
92	0,207369
93	0,234137
94	0,25449
95	0,279469
96	0,300265
97	0,335057
98	0,371225
99	0,401376
100	0,434615